HETEROGENEITY IN LONG-TERM TRAJECTORIES OF DEPRESSION: A REVIEW AND APPLICATION OF GROUP-BASED TRAJECTORY MODELING

By

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ABSTRACT

Objective: The goal of this dissertation was to study heterogeneity in long-term (i.e. 5+ year) trajectories of depression over time using group-based trajectory modeling – a statistical method designed to identify unobserved classes of individuals with different trajectory patterns. Paper 1 reviews studies that used group-based trajectory models (Latent Class Growth Analysis (LCGA) and Growth Mixture Modeling (GMM)) to examine heterogeneity in long-term trajectories of depressive symptoms (Chapter 2). In paper 2 we used LCGA to examine patterns and predictors of 10-year trajectories of inpatient and outpatient MDD treatment among patients with earlier onset (< 60) MDD (Chapter 3). In paper 3 we used LCGA to examine patterns and predictors of 5-year trajectories of inpatient and outpatient MDD treatment in late-onset (≥ 60) cases (Chapter 4).

Methods: Papers 2 and 3 used data from the Danish registers. The study sample in paper 2 consisted of 14,564 individuals born between 1935 and 1994. The study sample in paper 3 consisted of 12,200 individuals born between 1898 and 1947. Only individuals with no record of bipolar disorder or psychotic illness were eligible for inclusion in the study samples. Trajectories were estimated with LCGA using PROC TRAJ in SAS 9.4.

Results: We identified 4 classes with distinct trajectory patterns: *early recovery, prolonged initial illness, later recurrence* and *chronic illness.* Similar patterns were observed in early and late-onset cases, however the proportions of individuals in the prolonged initial illness and chronic illness classes were higher in late-onset cases. In cases with onset before 60, parental history of depression and anxiety predicted

membership in the later recurrence class, while parental history of psychotic illness predicted membership in the chronic illness class. In late-onset cases, past history of dementia predicted membership in the prolonged initial illness and chronic illness classes.

Conclusions: The majority of MDD cases in Denmark have a positive prognosis, however a significant minority of cases experience prolonged periods of illness. Demographic variables, characteristics of the initial diagnosis and parental history of psychiatric diagnoses predict course trajectory class membership. Differences in observable course trajectories may be indicative of underlying differences in genetic or biological etiology.

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CHAPTER 1: Introduction and Specific Aims

1.1 Depression: The Public Health Problem

Unipolar depression is a mental illness characterized by disturbances in mood, cognition, and vitality. Symptoms of depression include sadness, lack of interest or enjoyment, weight loss or weight gain, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue, feelings of worthlessness or inappropriate guilt, inability to concentrate, and recurrent thoughts of death or suicide (American Psychiatric Association [APA], 2013; World Health Organization [WHO], 1992). In its most severe form, Major Depressive Disorder (MDD), individuals report periods of 2 weeks or more in which they experience five or more of these symptoms most of the day, almost every day, along with marked impairment in social and/or occupation functioning (APA, 2013).

Depression is a leading cause of disability in both the developed and the developing worlds (Ferrari et al., 2013). According to the World Health Organization's 2010 Study of the Global Burden of Disease, mental and substance use disorders are the number one source of years lived with disability (YLD), with depression accounting for over 40% of the global burden of mental illness (Whiteford et al., 2013). MDD is the 11th leading cause of disability-adjusted life years (DALYs) worldwide and the 4th or 5th leading source of DALYs in high-income countries (Murray et al., 2012). Economically, the costs of depression are extremely high both to the individual and to society. In terms of direct costs, the U.S. and other high-income countries spend billions of dollars/euros on depression treatment each year (Sobocki, Lekander, Borgström, Ström, & Runeson,

2007; Tomonaga et al., 2013; Wang, Simon, & Kessler, 2003). In terms of indirect costs, depression is associated with increased use of the health care system for non-depression related care, lost productivity, missed work days, lower income and lower educational attainment (Donohue & Pincus, 2007; Kessler, 2012).

Although the bulk of the public health impact of depression is felt in terms of increased morbidity (i.e. disability), depression is also associated with increased mortality (Harris & Barraclough, 1998; Laursen, Munk-Olsen, Nordentoft, & Mortensen, 2007; Osby, Brandt, Correia, Ekbom, & Sparen, 2001). Depression is a risk factor for suicide (Nordentoft et al., 2013), and as of 2010, the Centers for Disease Control (CDC) ranked suicide as the 10th leading cause of death in the U.S. overall, and as one of the top five leading causes of death among individuals 10-54 years old (Centers for Disease Control and Prevention [CDC], 2010). Psychological autopsies suggest that 90% of completed suicides occur in individuals with a mental disorder, the most common of which being depression (Cavanaugh, Carson, Sharpe, & Lawrie, 2003; Fleischmann, Bertolote, Belfer, & Beautrais, 2005). Preventing and treating depression has been suggested as a method of suicide prevention among adolescents (Swartz et al., 2010). Depression is also associated with increased mortality among individuals suffering from somatic illnesses such as cardiovascular disease (Frasure-Smith & Lesperance, 2010; Goldston & Baillie, 2008; Rudisch & Nemeroff, 2003; Van der Kooy et al., 2007) and stroke (Pan, Sun, Okereke, Rexrode, & Hu, 2011).

1.2 Epidemiology of Depression: Prevalence, Predictors and Correlates

Depression is a common mental health problem, affecting approximately 5-10% of the U.S. population each year and around 14-21% at some point during their lifetimes

(Blanco et al., 2010; Hasin, Goodwin, Stinson, & Grant, 2005; Kessler et al., 2003; Kessler, Chiu, Demler, Merikangas, & Walters, 2005; Kessler et al., 2005). Outside of the U.S. the prevalence of depression is roughly similar, although there is significant variation between countries: estimates of the global 12-month prevalence of mood disorders (unipolar and bipolar) range from 5-7% in Latin America, 4-9% in Europe, 1-7% in Africa and the Middle East and 2-3% in Asia (WHO, 2004). In general, global estimates suggest that depression prevalence is highest in the U.S. and Western Europe, lower in Asian countries and highly variable (no doubt due to a combination of measurement issues and geo-political conflict) in the developing world (Bromet et al., 2011; Ferrari et al., 2013).

Demographic factors associated with depression include female gender (Weissman, Leaf, Holzer, Myers, & Tischler, 1984; Weissman & Klerman, 1985), Caucasian race (Riolo, Nguyen, Greden, & King, 2005) and lower socioeconomic status (Dohrenwend, Levav, Shrout, & Schwartz, 1992; Lorant et al., 2003). Childhood sexual abuse (Molnar, Buka, & Kessler, 2001), stressful life events (Kessler, 1997; Mazure, 1998) and chronic stressors (Hammen, 2005) are also robust predictors of depression. Finally, depression is known to run in families: family studies in clinical (Gershon et al., 1982; Mitchell, McCauley, Burke, Calderon, & Schloredt, 1989; Orvaschel, Walsh-Allis, & Ye, 1988; Puig-Antich et al., 1989; Weissman, Kidd, & Prusoff, 1982; Weissman, Gershon et al., 1984; Weller et al., 1994; Welner & Rice, 1988) and community (Beardslee, Keller, Lavori, & Klerman, 1988; Kendler, Davis, & Kessler, 1997; Klein, Lewinsohn, Rohde, Seeley, & Olino, 2005; Klein, Lewinsohn, Seeley, & Rohde, 2001; Low et al., 2012) samples suggest that the odds of having a first-degree relative with

depression are 2-3 times higher among depressed individuals compared with control subjects. Prospective studies suggest that the risk of depression among children of depressed parents is 2-3 times higher than the risk of depression in the children of controls (Beardslee et al., 1996; Hammen, Burge, Burney, & Adrian, 1990; Lieb, Isensee, Hofler, Pfister, & Wittchen, 2002; Radke-Yarrow, Nottelmann, Martinez, & Fox, 1993; Weissman, Warner, Wickramaratne, Moreau, & Olfson, 1997; Weissman et al., 2006).

Twin studies show that depression is 30-40% heritable (Sullivan, Neale, & Kendler, 2000), meaning that 30-40% of the population-level variation in depression can be attributed to genetic factors. Despite this, efforts to identify specific genes or genetic variables that confer risk for depression have met with limited success. Candidate gene studies, which look at the association between depression and a specific gene chosen for its biological relevance, have reported statistically significant findings in the literature, but these findings have proven difficult to replicate (Bosker et al., 2011). To date, at least eleven genome-wide association studies (GWAS) have been conducted looking at associations between depression and genetic variants across the genome (Hek et al., 2013; Kohli et al., 2011; Lewis et al., 2010; Muglia et al., 2010; Rietschel et al., 2010; Ripke et al., 2013; Shi et al., 2011; Shyn et al., 2011; Terracciano et al., 2010; Wray et al., 2012). None have succeeded in identifying replicable associations. As such, depression lags behind other mental disorders such as schizophrenia, for which over 100 significant variants have already been identified (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). Proposed explanations for the lack of genetic findings in depression include insufficient statistical power, un-modeled gene-X-environment interactions and genetic heterogeneity (Levinson et al., 2014).

Relative to other psychiatric disorders of similar levels of severity, unipolar depression is characterized by a large amount of phenotypic heterogeneity (i.e. heterogeneity in observable traits). This heterogeneity is so pronounced that it has led many clinicians and researchers over the years to suggest that depression is not a single disorder, but rather a nosological umbrella encompassing multiple disorders with potentially distinct etiologies. Early in the study of psychiatric disorders clinicians made a distinction between 'endogenous' depression, which was believed to arise spontaneously and be characterized by more severe or vegetative symptoms, and 'reactive' depression, which was believed to arise only in response to a stressful experience and was seen more as a maladaptive reaction to external stimuli rather than as an organic illness (Horwitz & Wakefield, 2007). The endogenous subtype persists today in the form of the specifier 'with melancholic features' in the Diagnostic and Statistical Manual of Mental Disorders 5th Edition (DSM-5) criteria for MDD (APA, 2013). The concept of reactive depression as a distinct depression subtype has fallen out of favor, however. An additional distinction has been suggested between what is termed 'typical' depression, characterized by insomnia and decreased appetite/weight loss vs. 'atypical' depression, characterized by hypersomnia and increased appetite/weight gain (Chen, Eaton, Gallo, & Nestadt, 2000; Kendler et al., 1996). These subtypes also persist today in the form of the MDD specifier 'with atypical features" (APA, 2013).

Clinicians and researchers also recognize the importance of heterogeneity in depression trajectories over time. Both the Internal Classification of Diseases 10th Edition (ICD-10) and the DSM-5 make a distinction between a diagnosis of MDD, in which symptoms are episodic and severe, and a diagnosis of dysthymia, in which

symptoms are chronic and mild. In addition, the DSM includes specifiers to indicate depression that occurs only during the autumn and winter months (e.g. 'with seasonal pattern') or within the context of a pregnancy (e.g. 'with peripartum onset') (APA, 2013). Premenstrual dysphoric disorder (PDD), a recent addition to the DSM, refers to a subtype of depression in which symptoms occur only during the premenstrual period (APA, 2013). Despite these efforts to differentiate depressed individuals based on differences in the timing of symptom presentation, there remains a large amount of heterogeneity in depression trajectories over time among individuals who fall within the same diagnostic categories. The remainder of this chapter will focus on describing what is currently known about heterogeneity in long-term trajectories of depression over time.

1.3 Long-term trajectories of depression over time

Opinions vary on what constitutes 'long-term', but for our purposes, 'long-term' is defined as 5 or more years. Literature on the long-term trajectories of depression fall within two categories: studies of long-term illness course in clinical cases (i.e., patients receiving treatment for depression in hospital or clinic settings) and studies of long-term trajectories of depressive symptoms in general population samples.

Depression course in clinical cases

The term c*ourse* refers to the period in the natural history of an illness between the onset of clinical symptoms (i.e. the point at which symptoms first cross the diagnostic threshold) and the ultimate outcome (death or recovery). Course is the "ebbing and flowing of psychopathology" (Eaton, 2002, pg. 216); the extent to which symptoms persist, remit and recur over time. The earliest studies of depression course relied on a set of 'change points' to characterize the course of depression over time: These change

points are *response* (aka partial remission), *remission, relapse, recovery* and *recurrence* (Frank et al., 1991).

An episode of major depression refers to the period in time during which an individual meets the full diagnostic criteria for MDD as specified in the ICD or the DSM. If treatment is successful, an individual will experience a *response,* at which point, although symptoms are still present to some degree, the criteria for disorder are no longer met. This is also known as partial remission. If the response is reversed and the individual once again meets the full diagnostic criteria for disorder he or she is said to have *relapsed.* In this case, the relapse is considered part of the initial episode. An individual is considered to be in *remission* once his or her symptoms are no longer present. Both full and partial remission can occur spontaneously, or in response to treatment. Remission typically indicates that the episode has ended, but if symptoms return within a specified amount of time (usually 8 weeks), the individual is once again said to have relapsed. If symptoms do not return within this specified amount of time, the individual has *recovered* from the episode. If at some point in the future the individual once again meets the diagnostic criteria for clinical illness, this is considered a *recurrence.* A recurrence, unlike a relapse, represents a new episode, distinct from previous episodes (Boland & Keller, 2009; Frank et al., 1991). Figure 1.1 illustrates the relationship between the 5 change points.

Figure 1.1: *Changes points used to study the course of depression in clinical samples*

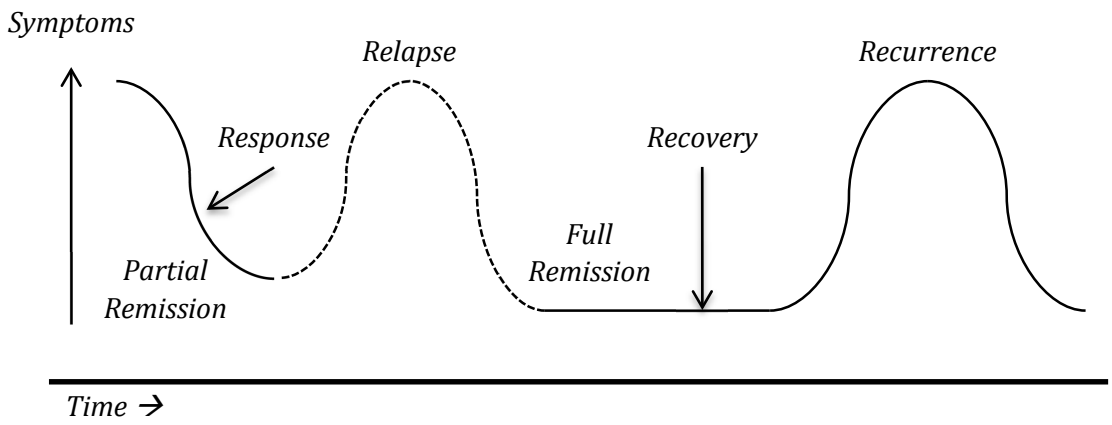


Figure Adapted from Boland & Keller, 2009

The establishment of consistent definitions of course change points allowed researchers to investigate the long-term course of depression by looking at outcomes such as number of episodes, time to relapse, time to recovery (i.e. episode duration) and time to recurrence. Long-term depression course has been studied in clinical samples including the Collaborative Depression Studies (CDS; (Keller et al., 1992; Mueller et al., 1996; Mueller et al., 1999; Solomon et al., 2000; Solomon et al., 1997; Solomon et al., 2008) and the Zurich study (Angst, Gamma, Sellaro, Lavori, & Zhang, 2003), community samples including the Lundby Study (Mattisson, Bogren, Horstmann, Munk-Jorgensen, & Nettelbladt, 2007), The Zurich Cohort Study (Angst, Gamma, Rossler, Ajdacic, & Klein, 2009; Merikangas et al., 2003), and the Epidemiologic Catchment Area Study (ECA; (Eaton et al., 1997; Eaton et al., 2008) and registry samples including the Danish Psychiatric Central Research Registry (Kessing, Mortensen, & Bolwig, 1998a; Kessing, Olsen, & Andersen, 1999; Kessing & Mortensen, 1999; Kessing, Hansen, Andersen, & Angst, 2004; Kessing, 1998; Kessing, Andersen, Mortensen, & Bolwig, 1998; Kessing, Andersen, & Mortensen, 1998; Kessing, Mortensen, & Bolwig, 1998b; Kessing & Andersen, 1999; Kessing, 1999; Kessing, Andersen, & Andersen, 2000; Kessing, Hansen, & Andersen, 2004).

Recovery. Studies suggest that around 50% of cases recover from an episode of depression within 3-6 months, and around 70-80% recover within 1 year (Angst et al., 2003; Eaton et al., 1997; Keller et al., 1992; Solomon et al., 1997; Spijker et al., 2002). Between 6-15% of cases, however, become depressed and stay depressed for as long as 20 years (Angst et al., 2009; Eaton et al., 2008; Mueller et al., 1996). Time to recovery remained consistent from episode to episode in several (Kessing & Mortensen, 1999;

Solomon et al., 1997) but not all (Eaton et al., 1997) studies. Higher morbidity, psychosocial impairment, never being married and longer duration of illness before treatment are associated with decreased odds of recovery (Solomon et al., 2008). Female gender was also associated with greater time to recovery (Kessing & Mortensen, 1999).

Relapse. Relapse rates reported in the literature range from 11-30% (Boland & Keller, 2009). The risk of relapse increases with each additional episode, particularly in women, even when patients have access to antidepressant medications such as SSRIs and SNRIs (Kessing et al., 2004).

Recurrence. Studies suggest that the rate of recurrence among individuals with a previous depression episode is around 40-50% in community samples (Eaton et al., 2008; Mattisson et al., 2007; Rhebergen et al., 2011) and around 70-90% in clinical samples (Boland & Keller, 2009; Mueller et al., 1999). Among clinical cases, 40% experience a recurrence within 2 years and 60% experience a recurrence within 5 years of their initial episode (Solomon et al., 2000). In community cases, median time to recurrence is 4 years (Mattisson et al., 2007). Time to recurrence decreases over the course of illness regardless of age or gender (Kessing, 1998; Kessing et al., 1998; Solomon et al., 2000), which is consistent with the ideas of sensitization and kindling (Monroe & Harkness, 2005; Post, 1992). Risk factors for recurrence include female gender, never having been married, longer duration of illness before treatment, shorter time since the last episode and comorbid alcoholism, (although with the exception of time since last episode, the effects of these predictors lessen as the disorder progresses) (Kessing et al., 1998; Kessing, 1999; Mueller et al., 1999). Higher number of previous episodes is also a risk factor for recurrence (Kessing & Andersen, 1999; Solomon et al., 2000) and the more

episodes a patient has, the shorter the time between episodes becomes (Somolon et al., 2000).

Trajectories of depressive symptoms in general population samples

The change points (relapse, recovery, recurrence etc.) used to characterize course in clinical samples are not relevant for studies of trajectories of depressive symptoms in the general population, as these studies lack the element of the diagnostic threshold upon which the change points are all based. Instead, studies of long-term depression trajectories in general population samples model trajectories of depressive symptoms over time using analytic techniques including hierarchical (a.k.a multi-level) linear models (Bryk & Raudenbush, 1987) and latent growth curve models (Willett & Sayer, 1994). Hierarchical linear models are an extension of standard regression in which two sources of variation are modeled: variation between individuals, and variation within individuals over time. Latent growth curve models are a type of structural equation model in which observed indicator variables (e.g. mean depressive symptoms at a series of time points) can be used to make inferences about the intercept (initial status) and slope (rate of change) of trajectories of depressive symptoms over time.

The most comprehensive study conducted to date on trajectories of depressive symptoms in a general population sample followed 2,320 individuals aged 19-95 years from the Baltimore Longitudinal study of Aging (Sutin et al., 2013). Results of hierarchical linear models showed that depressive symptom trajectories follow a U-shaped pattern: symptoms begin at a higher level in early adulthood, decrease steadily with age until 60-70, and then begin to increase again. Women had higher levels of

depressive symptoms than men at all ages, but this disparity lessened significantly in older adulthood.

A number of studies have focused exclusively on depressive symptom trajectories in adolescents and young adults within a developmental framework. All studies of depression trajectories in adolescents that examined gender differences found higher rates of depressive symptoms in females compared to males. Many of these studies also found that the rate of change in depressive symptoms in adolescents (ages 12-17) increased over time for girls and remained stable or decreased for boys (Garber, Keiley, & Martin, 2002; Ge, Natsuaki, & Conger, 2006; Kim, Capaldi, & Stoolmiller, 2003). Several studies found parallel increasing trajectories for males and females, however (Guo & Tillman, 2009; Natsuaki, Biehl, & Ge, 2009). As adolescents transition into emerging adults (ages 18-25), depressive symptoms appear to decline for both males and females (Adkins, Wang, & Elder, 2009; Galambos, Barker, & Krahn, 2006; Ge et al., 2006; Meadows, Brown, & Elder, 2006; Wickrama, Conger, Lorenz, & Jung, 2008), resulting in a curvilinear trajectory from early adolescence to emerging adulthood.

Studies have also examined trajectories of depressive symptoms exclusively in older adults. Results suggest that depressive symptoms in later life increase with age in a positive, linear fashion (Burns et al., 2013; Yang, 2007), although this effect may be due at least in part to cohort differences rather than age (Yang, 2007). Results also suggest that women consistently have higher levels of late-life depression than men (Burns et al., 2013; Glei, Goldman, Liu, & Weinstein, 2013). This may be due in part to differences in social position (Glei et al., 2013).

To my knowledge, only one study has used growth curve modeling to examine course trajectories in individuals with an actual unipolar depression diagnosis: Klein and colleagues (Klein, Shankman, & Rose, 2008) examined predictors of 10-year course trajectory of early onset dysthymic disorder and double depression in a sample of 87 outpatients. They found that older age, lower education, comorbid anxiety, family history of chronic depression, poor relationship with mothers and childhood sexual abuse predicted higher depressive symptoms at the 10 year mark.

1.4 Heterogeneity in depression trajectories

The studies discussed so far all employed analytic methods that assume individual trajectories revolve around a single population mean. The findings of these studies, however, suggest that trajectories of depression over time are highly variable. In clinical samples, studies suggest that some individuals experience only a single, brief episode during their lifetimes, others experience course trajectories characterized by fairly quick recovery followed by frequent relapses or recurrences, and a small but notable minority experience episodes that last for years or even decades (Angst et al., 2009; Eaton et al., 2008). Individual differences in intercepts and rates of change in general population samples also indicate the presence of latent sub-groups with distinct trajectory patterns (Sutin et al., 2013). There are statistical methods designed specifically to model trajectories of growth, accounting for the presence of sub-groups within a population. These methods are known as group-based trajectory models.

Group-based trajectory models

Group-based trajectory models are a type of structural equation model in which a response variable measured repeatedly over time (Y1, Y2…Y*i*) is used to characterize

trajectories separately for different latent groups (classes) of individuals within the sample (Muthen, 2004; Wang & Bodner, 2007). Unlike latent growth curve models, group-based trajectory models do not assume that the trajectory of growth within a population varies around a single population mean. Rather, they assume that the population in question is in fact composed of homogenous (or at least more homogenous) sub-populations with different trajectory parameters (Wang & Bodner, 2007). Rather than modeling the trajectory of the population as a whole, this method identifies groups following distinct trajectories over time and estimates trajectory parameters separately for each group. Types of group-based trajectory models include Latent Class Growth Analysis (LCGA; also known as semi-parametric group-based modeling (Jung & Wickrama, 2008; Nagin & Land, 1993; Nagin, 1999; Roeder, Lynch, & Nagin, 1999), in which within-group variation is assumed to be 0, and Growth Mixture Models (Muthen, 2004), in which within-group variation can be incorporated as a random effect. Both types of models allow for the incorporation of predictor variables (X1, X2…X*i*) of latent trajectory class membership.

Figure 1.2 shows a diagram of a hypothetical group-based trajectory model. Per convention, squares are used to denote observed variables and circles are used to denote latent variables. Parameters of an unconditional group-based trajectory model (i.e. a model without predictor variables) include the probability of membership in a given trajectory class as well as the slope (π_0) and intercept (π_1) for each class. Parameters of a conditional group-based trajectory model (i.e. a model which includes predictor variables) include the parameters described above as well as the log odds ratio for each predictor variable of membership in a given trajectory class relative to a reference class.

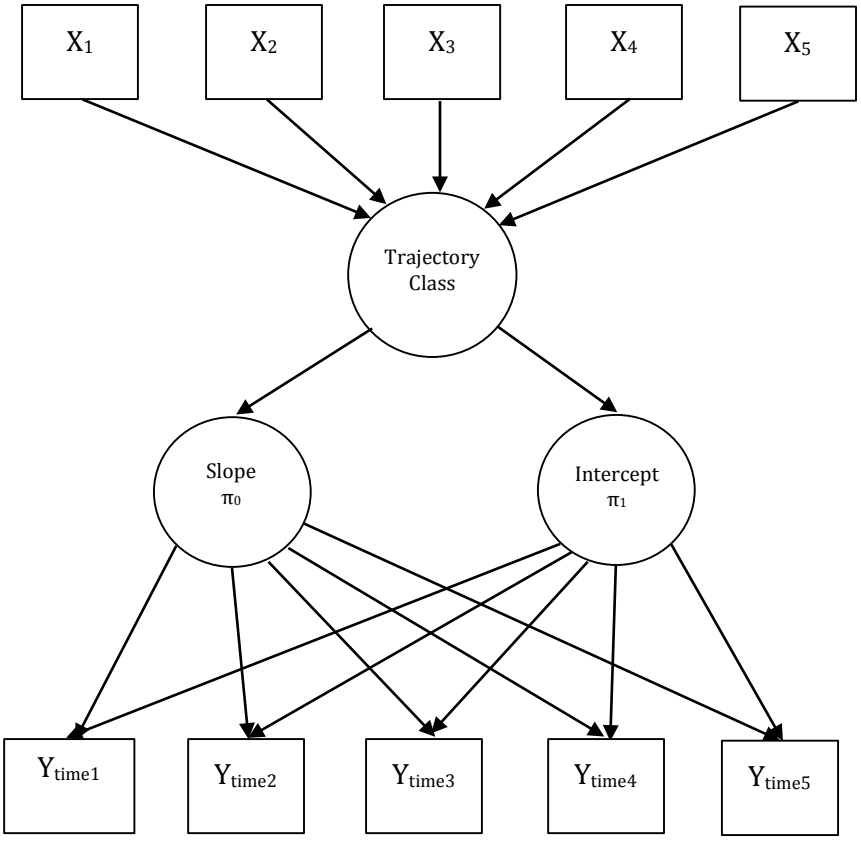
The probability of a particular pattern of responses on the observed variables used to estimate the trajectories (Y1, Y2…Y*i*) is equal to the sum across all latent trajectory classes (z_i) of the probability of class membership times the probability of the response pattern conditional on class membership. To put this in mathematical terms, if $\mathbf{Y}_i$ represents the response vector for a given individual and Z represents latent class membership, then:

$$P(Y_i) = \sum_{z=1}^{Z} P(Z = z)P(Y_i \,|Z = z)$$

In a model that includes covariates (X1, X2…X*i*), the probability of a particular response pattern $\mathbf{Y}_i$ conditional on levels of a set of covariates $\mathbf{X}_i$ is equal to the sum across all latent trajectory classes (z_i) of the probability of class membership conditional on the covariates, times the probability of the response pattern conditional on class membership. In mathematical terms, this means that:

$$P(Y_i \,|X_i) = \sum_{z=1}^{Z} P(Z = z|X_i)P(Y_i|Z = z)$$

Figure 1.2: *Group-based Trajectory Model Diagram*



1.5 Specific Aims

The goals of this dissertation project were to review findings from studies that used group-based trajectory modeling to examine heterogeneity in long-term (i.e. 5+ years) trajectories of depression over time, and to apply this method to examine long-term trajectories of MDD admissions in the Danish Psychiatric Research Registry. Group-based trajectory models require large sample sizes in order to accurately and precisely characterize trajectory patterns for multiple subgroups within a population. In addition, studying long-term trajectories requires many years of follow-up data on the same individuals. The Danish psychiatric registry, which includes the entire population of Denmark (~ 8 million people), is one of the few data sources available that meets both of these requirements.

The specific aims of this project were as follows:

1) **Aim 1:** Conduct a systematic review of the literature to identify, summarize and compare studies that have used group-based trajectory modeling to characterize heterogeneity in long-term trajectories of depression over time.
    a. Identify predictors and correlates of course trajectory class membership
    b. Identify outcomes associated with course trajectory class membership
2) **Aim 2:** Use latent class growth analysis to characterize heterogeneity in 10-year course trajectories of MDD (first onset at < 60 years of age) using inpatient and outpatient treatment records from the Danish Psychiatric Research Registry
    a. Examine potential predictors of course trajectory class membership including:

i. Demographic characteristics (gender, place of birth (urban, rural, other), birth year)
ii. Characteristics of the first MDD diagnosis (calendar year of first admission, severity of first admission (mild, moderate, severe without psychotic features, severe with psychotic features), inpatient treatment at first diagnosis and past history of suicide attempt/self-harm)
iii. Parental history of psychiatric diagnoses (unipolar depression, bipolar disorder, non-affective psychotic illness, substance abuse and anxiety)

3) **Aim 3:** Use latent class growth analysis to examine heterogeneity in 5-year course trajectories of late-onset MDD (i.e., first onset at ≥ 60 year of age) using inpatient and outpatient treatment records in the Danish Psychiatric Research Registry
   a. Examine potential predictors of course trajectory class membership including:
      i. Demographic characteristics (gender, place of birth (urban, rural, other), birth year)
      ii. Characteristics of the first MDD diagnosis (calendar year of first admission, severity of first admission (mild, moderate, severe without psychotic features, severe with psychotic features), inpatient treatment at first admission and past history of suicide attempt/self-harm)

iii. Past history of somatic diagnoses (vascular disease (heart disease, diabetes, hypertension, stroke), cancer, rheumatoid arthritis and dementia)

The decision to examine trajectories separately in individuals with age of onset below 60 and age of onset above 60 was made based on a combination of substantive and practical considerations. Substantively, research suggests that there may be etiologic and phenotypic differences in depression depending on when it first manifests. Studies from clinical (Pedersen et al., 2014) and community (Eaton et al., 1997) samples suggest that the age of onset distribution for MDD is bimodal, with one peak in early adulthood and a second, smaller peak in late adulthood. Studies also suggest that late onset depression may have a smaller genetic component than early onset depression (Grayson & Thomas, 2013; Musliner et al., 2015; Weissman, Wickramaratne et al., 1984). Researchers have also posited that a subset of late onset depression cases are due to vascular pathologies (i.e., pathology of the circulatory system) that lead to brain lesions, visible on MRI scans as white matter hyperintensities (Alexopoulos et al., 1997a; Alexopoulos et al., 1997b; Alexopoulos, 2006; Taylor, Aizenstein, & Alexopoulos, 2013). Some evidence also suggests that course may be different in early vs. late onset cases: Mueller et al. (Mueller et al., 2004) examined time to MDD recovery and recurrence in different age groups and found that while time to recovery was not statistically different, time to recurrence was significantly shorter among older adults.

Practically, there were several methodological considerations that made examining trajectories separately for earlier vs. late onset MDD cases preferable. First, a primary goal of Aim 2 was to examine the impact of parental history of psychiatric

diagnosis on the probably of course trajectory class membership. Links to parents are reliably available in the Danish Civil Registry for individuals born after 1955, however individuals with late-onset MDD were born between 1898 and 1947, meaning there were no links to parents for the majority of these individuals. Though it was not possible to examine the impact of parental psychiatric disorders on course trajectories of late-onset MDD, it was possible to examine the impact of somatic illness, which is the main thrust of Aim 3.

Second, attrition due to death was predictably higher among individuals with late-onset MDD, therefore we chose to limit the follow-up period to 5-years among late-onset cases in order to reduce attrition due to mortality. To facilitate comparisons between early and late onset MDD cases I conducted an additional analysis, separate from analyses conducted for the papers described in chapters 3 and 4, looking at 5-year course trajectories in early-onset cases using the same sample selection pipeline as was used to select late-onset cases in aim 3. The results of this analysis, along with a comparison between trajectory patterns in early and late onset MDD cases, are described in the overall discussion chapter (Chapter 5).

The remainder of this dissertation is structured as follows: Chapter 2 describes the systematic review of the literature outlined in Aim 1. Chapter 3 describes patterns and predictors of 10-year course trajectories of MDD (Aim 2). Chapter 4 describes patterns and predictors of 5-year course trajectories of late-onset MDD (Aim 3), and Chapter 5 provides a summary and discussion of the results of the three aims along with implications and directions for future research.

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CHAPTER 2: Review of evidence from group-based trajectory models

2.1 Abstract

Background: Different groups of individuals may follow different depression trajectories over time. Group-based trajectory models (i.e. growth mixture models, latent class growth analysis), are designed to identify trajectories separately for different sub-groups within a population. The goal of this paper was to review studies that used these methods to examine heterogeneity in long-term trajectories of depression and summarize a) the numbers and patterns of trajectories and b) antecedents and outcomes associated with trajectory class membership.

Methods: W conducted a systematic review of literature in the Medline and PsychINFO databases. Articles were included if they a) modeled trajectories of depression, b) used a group-based trajectory model approach, c) followed participants for 5+ years and d) had a sample size of at least 200.

Results: We identified 26 studies from 25 separate cohorts. Most of the studies identified either 4 or 6 trajectory classes. Trajectories varied in terms of severity (mild, moderate, severe) and stability (stable, increasing, decreasing). In most studies, the majority of participants had consistently low depressive symptoms, but a notable minority (usually < 10%) had persistently high symptoms. Predictors of trajectories with greater symptom burden included female gender, lower income/education and non-white race. Other predictors were specific to different populations (i.e. mothers, older adults). High symptom burden trajectories were associated with poor psychiatric and psychosocial outcomes.

Limitations: Comparisons between studies were entirely qualitative.

Conclusions: Trajectories of depression symptoms are heterogeneous, with most individuals showing minimal symptoms but a notable minority experiencing chronic high symptom burden.

Key words: review, depression, depressive symptoms, trajectories, group-based trajectory modeling, growth mixture modeling, latent class growth analysis

2.2 Introduction

In order to fully elucidate the nature of a disorder, mental or physical, it is important to understand how that disorder changes over time. Do symptoms remain stable or do they fluctuate? When symptoms do remit, what is the likelihood that they will return and if so, how soon is this likely to occur?

There are a variety of statistical methods designed to address these types of research questions. Survival analyses such as Kaplan Meier Curves (Kaplan & Meier, 1958), Cox Proportional Hazard Models (Cox, 1972) and Poisson regression models (Andersen, Borgen, Gill, & Keiding, 1993) are used when the outcome of interest is the time to a particular event. Hierarchical linear models (Bryk & Raudenbush, 1987) extend the traditional regression framework to allow for the partitioning of two sources of variance: variation between individuals and variation within an individual over time (i.e. growth curves). Latent Growth Curve Models (Willett & Sayer, 1994), a type of structural equation model, use observed indicator variables to make inferences about the intercept (initial status) and slope (rate of change) of trajectories over time.

All of these methods operate under the assumption that the individual trajectories of people within a given population revolve around a single population mean. In some instances this assumption is most certainly reasonable, however in the case of depression, this assumption is unlikely to be accurate. Studies of long-term trajectories of depressive symptoms among individuals with major depressive disorder (MDD) suggest that some individuals experience only a single, brief episode during their lifetimes, others experience courses characterized by fairly quick recovery followed by frequent relapses or recurrences, and a small but notable minority experience episodes that last for years or

even decades (Angst, Gamma, Rossler, Ajdacic, & Klein, 2009; Eaton et al., 2008; Mueller et al., 1996; Mueller et al., 1999; Solomon et al., 2000; Solomon et al., 1997; Solomon et al., 2008). Individual differences in intercepts and rates of change suggest that there is also heterogeneity in trajectories of depressive symptoms among individuals without a depression diagnosis (Sutin et al., 2013).

There are statistical methods, known collectively as group-based trajectory models, which can be used to identify patterns of trajectories separately for different sub-groups within a population. Group-based trajectory models are latent variable models, meaning they use correlations between observed (i.e. indicator) variables to make inferences about unobserved (i.e. latent) variables, such as membership in an unobserved class (Bartholomew & Knott, 1999). Unlike hierarchical linear models and latent growth curve models, group-based trajectory models do not assume that the trajectory of growth within a population varies around a single mean. Rather, they assume that the population in question is in fact composed of homogenous (or at least more homogenous) sub-populations with different trajectory parameters (Wang & Bodner, 2007). Rather than modeling the trajectory of the population as a whole, this method identifies groups following distinct trajectories over time and estimates trajectory parameters separately for each group. Types of group-based mixture models include Latent Class Growth Analysis (LCGA; also known as semi-parametric group-based modeling (Jung & Wickrama, 2008; Nagin & Land, 1993; Nagin, 1999; Roeder, Lynch, & Nagin, 1999), in which within-group variation is assumed to be 0, and Growth Mixture Models (Muthen, 2004), in which within-group variation can be incorporated as a random effect. GMMs in which course trajectories are related to a distal outcome are referred to as General Growth

Mixture Models (GGMM). Parameters of group-based trajectory models include the probability of membership in a particular latent trajectory class for each individual, as well as the intercept and slope of the trajectory for each class.

The goal of this paper is to critically review studies that have used group-based trajectory models (GMM, GGMM or LCGA) to examine heterogeneity in long-term trajectories of depression. Opinions vary on what constitutes "long-term", but for our purposes, long-term is defined as 5 or more years. Of particular interest for this review were 1) the number of distinct trajectory patterns identified, 2) patterns of group-specific trajectories, 3) replicable predictors of membership in different course trajectory groups and 4) outcomes associated with course trajectory class membership.

2.3 Method

Identification of relevant literature

The initial search was conducted using the MEDLINE and PsychINFO databases via the Ebscohost search engine. The following search terms were used: (depression OR depressive symptoms) AND (trajectories OR latent class growth analysis OR growth mixture model OR semi-parametric group-based modeling). We restricted the search to articles published in English in peer-reviewed journals between 1999 and June 2015. This search yielded 1,231 results. The titles, abstracts and, where appropriate, manuscripts of the resulting records were then reviewed by the first author to determine whether each study met criteria for inclusion in the review. Finally, the reference lists of relevant articles were reviewed to identify any papers that might have been missed in the initial search.

Selection criteria

Articles were included in the review if they met the following criteria: a) The response variable in the trajectory analysis was depression or depressive symptoms (as opposed to internalizing problems, for example), b) the length of follow-up was at least 5 years, c) the study employed a group-based trajectory modeling approach (GMM, GGMM or LCGA) and d) the sample included at least 200 individuals.

The goal was to include articles similar enough in content and methodology to allow for straightforward comparison of the results. Because the vast majority of the studies that met criteria for inclusion used self-reported measures of depression, we chose not to include the two studies which used parental report rather than self-report to measure depressive symptoms (Dekker et al., 2007; Prinzie, van Harten, Dekovic, van den Akker, & Shiner, 2014). We also chose not to include studies of joint trajectories (i.e. depression and anxiety (Olino, Klein, Lewinsohn, Rohde, & Seeley, 2010), depression and substance abuse (Brook, Brook, & Zhang, 2014; Pahl, Brook, & Lee, 2014) or depression and delinquent or disruptive behavior (Brook, Lee, Finch, & Brook, 2014; Reinke, Eddy, Dishion, & Reid, 2012). Two additional studies were excluded because they focused on depressive symptoms within the context of adjustment in the wake of a stressful event, either a cancer diagnosis (Burton, Galatzer-Levy, & Bonanno, 2014) or bereavement in caregivers (Aneshensel, Botticello, & Yamamoto-Mitani, 2004).

2.4 Results

Study characteristics

We identified 26 studies from 25 separate samples that met the above criteria for inclusion in the review. Characteristics of these studies, including the country, sample

size, average age (or, in the case of school-based studies, grade) at baseline, percent female, length of follow-up, measure of depression, analytic method (GMM, GGMM, LCGA) and a description of the final model are shown in Table 2.1.

Length of follow-up ranged from 5 to 23 years and sample size ranged from 206 to 17,196 participants. Two of the studies modeled course trajectories among individuals with a clinical depression diagnosis. The remaining 24 studies modeled trajectories of depressive symptoms in general population samples without regard to clinical diagnosis. All but one study (Colman et al., 2011) modeled trajectories of depressive symptoms, while the remaining study modeled the probability of experiencing a recurrent episode. The majority of the studies were conducted in the US, although several other countries including Canada, Australia and Taiwan, were represented. Of the 26 studies included in the review, 1 study identified 2 trajectory classes, 7 studies identified 3 trajectory classes, 11 studies identified 4 trajectory classes, 4 studies identified 5 classes and 3 studies identified 6 trajectory classes. Seven of the 26 studies focused exclusively on depression trajectories in children/adolescents, 5 in adults, 6 in mothers and 8 in older adults.

The majority of the studies included information on both males and females, although 7 studies included only female participants (Byers et al., 2012; Campbell, Matestic, von Stauffenberg, Mohan, & Kirchner, 2007; Gross et al., 2009; Luomo et al, 2015; Matjasevich et al, 2015; van der Waerden et al, 2015; Wickham et al., 2015) and one study only included male participants (Stoolmiller, Kim, & Capaldi, 2005). The most common measure of depressive symptoms was the Centers for Epidemiologic Studies Depression Scale (CES-D).

Table 2.1: *Studies using group-based trajectory models to examine heterogeneity in long-term trajectories of depression by population*

Study	Country	Sample Size	Age/grade at Baseline	% Female	Length of Follow-Up/# of time points	Depression Measure/# of items	Analytic Method	Final Model
Children/Adolescents:								
Stoolmiller et al., 2005	USA	206	10.1 years	0%	10 years, 10 time points	CES-D (20 items)	GGMM	4 Classes: - Very low (5.8%) - Moderate-decreasing (34.0%) - High-decreasing (35.9%) - High-persistent (24.3%)
Costello et al., 2008	USA	11,559	7th grade	52%	13 years, 7 time points	CES-D (3 items)	LCGA	4 Classes: - Early high depressed mood (9.5%) - Late escalating depressed mood (2.4%) - Low depressed mood (59.4%) - No depressed mood (28.7%)
Mazza et al., 2010	USA	951	1st or 2nd grade	46%	6 years, 7 time points	Seattle Personality Questionnaire depression scale (6 items)	LCGA	5 Classes: Girls: - Moderately depressed risers (11.6%) - Moderately depressed changers (11.0%) - Mildly depressed stables (27.7%) - Low depressed risers (22.7%) - Low depressed stables (27.0%) Boys: - Moderately depressed risers (7.0%) - Moderately depressed changers (11.2%) - Mildly depressed stables (20.4%) - Low depressed risers (37.2%) - Low depressed stables (24.3%)

Table 2.1 *Continued*

Study	Country	Sample Size	Mean Age /grade at Baseline	% Female	Length of Follow-Up/# of time points	Depression Measure/# of items	Analytic Method	Final Model
Chaiton et al., 2013	Canada	1,293	12-13 years	52%	5 years, 20 time points	Depressive symptom scale (6 items)	LCGA	3 Classes: Boys: - High (14%) - Moderate (36%) - Low (50%) Girls: - High (28%) - Moderate (43%) - Low (29%)
Duchesne et al., 2013	Canada	414	12 years	55%	5 years, 6 time points	CIDI-S (5 items)	LCGA	4 Classes: - High declining (7.0%) - Moderate increasing (11.3%) - Moderate stable (54.6%) - Low stable (27.2%)
Mezulis et al., 2013	USA	382	11 years	52%	7 years, 8 time points	CIDI (27 items)	GMM	3 Classes: - Early high (12%) - Increasing (37%) - Stable low (51%)
Yaroslavsky et al., 2013	USA	719	17 years	59%	14 years, 10 time points	CES-D (20 items)	GMM	3 Classes: - High stable (32%) - Moderate decreasing (44%) - Low decreasing (24%)
Adults:								
Salmela-Aro et al., 2008	Finland	297	21 years	74%	10 years, 7 time points	BDI-R (13 items)	GMM	3 Classes: - High increasing (16%) - Moderate (61%) - Low (23%)

Table 2.1 *Continued*

Study	Country	Sample Size	Mean Age /grade at Baseline	% Female	Length of Follow-Up/# of time points	Depression Measure/# of items	Analytic Method	Final Model
Lincoln et al., 2010	USA	3,485	54 years (range: 25-75+ years)	63%	16 years, 4 time points	CES-D (11 items)	GMM	4 Classes: - Increasers (11%) - Slow decliners (15%) - High symptoms (5%) - Low symptoms (68%)
Colman, 2011	Canada	585	38 years	65%	6 years, 4 time points	CIDI-S	LCGA	2 Classes: - At least one recurrence (55.3%) - No recurrence (44.7%)
Cronkite et al., 2013	USA	382	40 years	55%	23 years 5 time points	Health and Daily Living Form (10 items)	LCGA	3 Classes: - Low severity (22.7%) - Moderate severity (49.5%) - High severity (27.8%)
Melchior et al., 2013	France	12,650	Range = 42 - 57 years)	26%	13 years, 5 time points	CES-D (20 items)	LCGA	4 Classes: Men: - No depression (72%) - Increasing depression (4.2%) - Decreasing depression (17.8%) - Persistent depression (6%) Women: - No depression (58.1%) - Intermittent depression (21.8%) - Decreasing depression (14%) - Persistent depression (6.1%)

Table 2.1 *Continued*

Study	Country	Sample Size	Mean Age /grade at Baseline	% Female	Length of Follow-Up/# of time points	Depression Measure/# of items	Analytic Method	Final Model
Mothers:								
Campbell et al., 2007	USA	1,261	28 years	100% (mothers)	7 years, 7 time points	CES-D (20 items)	LCGA	6 Classes: - High chronic (2.5%) - Moderate increasing (6.2%) - High decreasing (5.6%) - Intermittent (3.6%) - Moderate-stable (36%) - Low-stable (45.6%)
Gross et al., 2009	USA	289	28 years	100% (mothers)	8 years, 8 time points	BDI (21 items)	LCGA	4 Classes: - Low symptoms (25.2%) - Moderate low (46.7%) - Moderate high (21.8%) - High chronic (7.3%)
Luomo et al., 2015	Finland	329	27 years	100% (mothers)	16 years, 6 time points	EPDS (10 items)	LCGA	4 classes: - Very low (18%) - Low stable (53%) - High stable (27%) - Intermittent (3%)
Matjasevich et al., 2015	Brazil	3,332	26 years	100% (mothers)	6 years, 5 time points	EPDS	LCGA	5 Classes: - Low symptoms (34.8%) - Moderate low (40.9%) - Increasing (9%) - Decreasing (9.9% - High chronic (5.4%)

Table 2.1 *Continued*

Study	Country	Sample Size	Mean Age /grade at Baseline	% Female	Length of Follow-Up/# of time points	Depression Measure/# of items	Analytic Method	Final Model
Van der Waerden, 2015	France	1,807	30 years (median)	100% (mothers)	5 years 9 time points	CES-D/EPDS	LCGA	5 Classes: - No symptoms (60.2%) - Persistent intermediate (25.2%) - Persistent high (5%) - High, pregnancy only (4.7%) High, preschool only (4.9%)
Wickham et al., 2015	Canada	2,910	Unspecified	100% (mothers)	10 years, 6 time points	CES-D (12 items)	LCGA	5 Classes: - Low symptoms (47.9%) - Mild symptoms (36%) - Increasing symptoms (10.4%) - U shaped trajectory (4%) - Stable high symptoms (1.7%)
Older Adults:								
Andreescu et al., 2008	USA	1,260	75 years	61%	12 years, 6 time points	mCES-D (20 items)	LCGA	6 Classes: - Persisting symptoms (2.1%) - Remitting symptoms (4.8%) - Emerging symptoms (4.2%) - Stable low group (52.6%) - Stable asymptomatic group (28.1%) - Stable asymptomatic group (8.2%)
Liang et al., 2011	USA	17,196	64 years	59%	10 years, 5 time points	CES-D (9 items)	LCGA	6 Classes: - Minimal (15.9%) - Low (36.3%) - Moderate stable (29.2%) - High decreasing (6.6%) - Moderate increasing (8.3%) - Persistently high (3.6%)

Table 2.1 *Continued*

Study	Country	Sample Size	Mean Age /grade at Baseline	% Female	Length of Follow-Up/# of time points	Depression Measure/# of items	Analytic Method	Final Model
Kuo et al., 2011	Taiwan	3,922	68 years	43%	10 years, 4 time points	CES-D (10 items)	LCGA	4 Classes: - Persistent low (41.8%) - Persistent mild (46.8%) - Late peak (4.2%) - High chronic (7.2%)
Hsu et al., 2012	Taiwan	2,039	72 years	51%	18 years, 5 time points	CES-D (20 items)	LCGA	4 Classes: Males - Low (48.4%) - Medium (41.4%) - Increasing (7.4%) - Declining (2.7%) Females: - Low (35.6%) - Medium (38%) - Increasing (16.3%) - Declining (10.1%)
Byers et al., 2012	USA	7,240	73 years	100%	20 years, 4 time points	GDS-S (15 items)	LCGA	4 Classes: - Minimal (27.8%) - Persistently low (54%) - Increasing (14.8%) - Persistently high (3.4%)
Kuchibhatla et al., 2012	USA	4,162	74 years	65%	10 years, 4 time points	CES-D (20 items)	GGMM	4 Classes: - Stable low (76.6%) - Initially low, increasing (10%) - Stable high (5.4%) - Initially high, improving, reverting (8%)

Table 2.1 *Continued*

Study	Country	Sample Size	Mean Age /grade at Baseline	% Female	Length of Follow-Up/# of time points	Depression Measure/# of items	Analytic Method	Final Model
Montagnier et al., 2014	France	2,590	75 years	59%	20 years 20 time points*	CES-D (20 items)	LCGA	3 Classes: Males: - Never depressed (65%) - Emerging depression (28%) - Increasing depression (7%) Females: - Never depressed (56%) - Rising subclinical (33%) - Persistent depression (11%)
Hybels et al., 2015	USA	944	75 years	58.2%	10 years 6 time points	CES-D (8 items)	LCGA	3 Classes: - Minimal depressive symptoms (43%) - Low depressive symptoms (41%) - Moderate depressive symptoms (16%)

Depression measure abbreviations: BDI = Beck Depression Inventory, CES-D = Center for Epidemiologic Studies Depression Scale, CIDI = Children's Depression Inventory, CIDI-S = Children's Depression Inventory – Short Form, EDPS = Edinburgh Postnatal Depression scale, GDS-S = Geriatric Depression Scale – Short Form, HSC = Hopkins Symptoms Checklist, LIFE = Longitudinal Interval Follow-Up Evaluation, mCES-D = modified CES-D (yes/no items).
Analytic Method abbreviations: GGMM = Generalized Growth Mixture Model, GMM = Growth Mixture Model, LCGA = Latent Class Growth Analysis
*Analysis conducted using age as time-metric.

Patterns of long-term depression trajectories

Results of the studies illustrated in Table 2.1 suggest that long-term trajectories of depressive symptoms vary in terms of two characteristics: severity (mild, moderate severe) and stability (stable, increasing, decreasing). All of the studies reviewed here identified one or more classes characterized by stable low, minimal or mild symptoms. This group (or groups) was typically the largest trajectory class, containing over 45% of the sample in all but 5 (Cronkite et al., 2013; Duchesne & Ratelle, 2013; Salmela-Aro, Aunola, & Nurmi, 2008; Stoolmiller et al., 2005; Yaroslavsky et al., 2013) of the studies. Another trajectory pattern observed frequently was a trajectory characterized by persistently high depressive symptoms. This was almost always the smallest class, containing roughly 2.5-7% of the samples, although several studies (Chaiton et al., 2013; Cronkite et al., 2013; Luomo et al., 2013; Stoolmiller et al., 2005; Yaroslavsky et al., 2013) reported proportions as high as 24-32% in this group. Many of the studies also identified a group with moderate, stable symptoms ranging in size from 29-55% of the sample. Some of the studies identified groups of individuals with depressive symptoms that were unstable, either increasing or decreasing over time. These classes were mostly present in studies in which the final model contained 6 classes, and also tended to be on the smaller side (4-15%).

Gender differences

Five of the studies examined trajectories of depressive symptoms separately for males and females. Mazza et al. (2010) examined 6-year depression trajectories in 1st and 2nd graders and found similar trajectory patterns for boys and girls, but the proportion of participants in classes with more depressive symptoms was higher for girls than for boys.

Chaiton et al. (2013) examined 5-year trajectories in adolescents and found similar results: the same overall trajectory patterns in males and females, but more females in the high symptoms group. Melchior et al. (2013) examined 13-year trajectories in adults and again found similar patterns in men and women. They found equal numbers (6%) of men and women in the "persistent depression" class, but fewer women (58% vs. 72%) in the "no depression" class. Hsu et al. (2012) examined 18-year trajectories of depressive symptoms in older adults and again found similar patterns among males and females, but more females than males in the trajectory classes characterized by higher symptoms (64% vs. 51.5%). Finally, Montagnier et al. (2014) examined 20-year trajectories in older adults and found that while both groups contained a "no depression" class and an "increasing depression" class, the most symptomatic class in women displayed stable high symptoms over time, while the most symptomatic class in men exhibited a fluctuating pattern in which symptoms decreased slightly and then began to rise in a linear fashion with age. As with the other three studies, a higher proportion of women than of men fell within classes with higher depressive symptom burdens.

Age differences

There did not appear to be any consistent differences in terms of the number or patterns of depression trajectories by age group, however the proportion of the samples in chronic high depression symptom trajectory classes decreased with age, from 14-32% in adolescents to 2.5-27% in adults (including mothers) and finally 2.1-7.2% in older adults.

Racial/ethnic differences

Costello et al. (2008) examined race/ethnicity as a predictor of depression trajectory among students in the National Longitudinal Study of Adolescent Health (Add

Health). They found that black and Asian students were both more likely to be in the 'low depression' and 'early high depression' classes relative to the 'no depression' class, and Latino students were more likely to be in the 'early high depression' class relative to the 'no depression class'. Liang et al. (2011) examined race/ethnicity as a predictor of depression trajectory in older adults from the Health and Retirement Study (HRS). They found that black and Hispanic participants were more likely to be in the low, moderate, decreasing and increasing trajectory classes relative to the minimal depressive symptoms class. In contrast, Lincoln et al. (2010) examined heterogeneity in depressive symptom trajectories in black and white adults in the Americans' Changing Lives Study and did not find a statistically significant association between race and depression trajectory class membership, and Kuchibhatla et al. (2012) found a larger proportion of whites in the stable-high depression trajectory.

Predictors of trajectory group membership

Female gender was almost universally associated with membership in trajectory classes characterized by higher depressive symptoms. This is consistent with the studies that examined trajectories separately in males and females discussed above, in which trajectory patterns were similar across genders but the proportion of women in trajectories with higher symptoms was larger. Lower education (or in the case of children/adolescents, lower academic achievement) and lower income (or in the case of children/adolescents, lower family income) were also consistently associated with poor depression trajectories. Stressful life events were associated with membership in depression trajectories with higher symptom burdens in adolescents (Stoolmiller et al., 2005) and adults (Melchior et al., 2013) and older adults (Kuchibhatla et al., 2012) but

not in children (Mazza et al., 2010). Alcohol use was associated with higher symptom trajectories in adolescents (Costello et al., 2008; Yaroslavsky et al., 2013), but lower symptom trajectories in adults (Melchior et al., 2013). In older adults, ever consuming alcohol was found to be protective against a high-chronic symptom trajectory (Kuo et al., 2011) while daily alcohol consumption was not associated with trajectory class membership (Byers et al., 2012; Montagnier et al., 2014). Tobacco smoking was associated with poor depressive symptom trajectories in women but not in men (Byers et al., 2012; Melchior et al., 2013). Previous history of psychopathology, particularly previous history of depression, was associated with poor trajectories in all age groups (Andreescu et al., 2008; Costello et al., 2008; Duchesne & Ratelle, 2013; Hsu, 2012; Mazza et al., 2010; Montagnier et al., 2014; Stoolmiller et al., 2005; Yaroslavsky et al., 2013).

Additional predictors of trajectories characterized by higher symptom burdens in adolescents (Table 2.2) include problems with peer relationships such as peer rejection, lack of social competency or lack of connection with friends (Costello et al., 2008; Mazza et al., 2010; Yaroslavsky et al., 2013) as well as problems with family relationships including family conflict or lack of connection/attachment to parents (Costello et al., 2008; Duchesne & Ratelle, 2013). Parental depressive symptoms (Stoolmiller et al., 2005) and parental history of major depressive disorder (Yaroslavsky et al., 2013) were also predictive of higher symptom burden trajectories in adolescents. Other predictors of trajectories with high symptom burden in adolescents included lack of self-esteem (Costello et al., 2008), rumination (Mezulis et al., 2013), loneliness (Yaroslavsky et al., 2013), poor coping skills (Yaroslavsky et al., 2013) and early puberty (Mezulis et al.,

2013). Means and odds ratios for most predictor variables followed a dose-response-like pattern, such that as the severity of the trajectory increased, so did the mean or odds ratio for that predictor variable. For example, Stoolmiller et al. (2005) found that average family income was $28,921 among children in the very-low symptom group, $21,316 in the moderate-decreasing group, $17,634 in the high decreasing group and $15,679 in the high-persistent group.

Studies of depression trajectories in mothers (Table 2.3) examined risk factors related to characteristics of both the mother and the child. Characteristics related to the mother associated with maternal trajectories with higher symptom burdens included younger maternal age and marital instability/poor marital relationship quality (Campbell et al., 2007), past history of mental health problems, anxiety during pregnancy Luomo et al., 2015; van der Waerden et al., 2015), overinvestment in work and a past history of childhood adversity (van der Waerden et al., 2015), poor life satisfaction, loneliness and a poor relationship with the child's grandmother (Luomo et al., 2015). Noncompliance in the child was associated with higher symptom trajectories in the mother (Gross et al., 2009). As with adolescents, there was an overall dose-response-like relationship between most predictor variables and trajectory. For example, Campbell et al. (2007) found that the proportion of women with stable marriages across the entire follow-up period was 82.3% in the low-stable group, 60% in the moderate-stable and intermittent groups, 43% in the moderate increasing and high-decreasing groups, and 38.7% in the high-chronic group.

Predictors of trajectories with higher symptom burden in older adults (Table 2.4) included poor self-rated health (Kuchibhatla et al., 2012; Kuo et al., 2011; Liang et al.,

2011) number of chronic somatic diseases at baseline (Hsu, 2012; Kuo et al., 2011; Liang et al., 2011), past history of ischemic heart disease or stroke (Byers et al., 2012; Montagnier et al., 2014), diabetes, hypertension, obesity and breast cancer (Byers et al., 2012). Functional impairment was a robust predictor of higher symptom trajectory across a number of studies (Andreescu et al., 2008; Byers et al., 2012; Hsu, 2012; Kuchibhatla et al., 2012; Montagnier et al., 2014), but the evidence for cognitive impairment was mixed, with two studies reporting no effect of cognitive impairment on depression trajectory class membership (Byers et al., 2012; Kuo et al., 2011) and three studies reporting that it increases risk for membership in a trajectory class with a higher symptom burden (Andreescu et al., 2008; Kuchibhatla et al., 2012; Montagnier et al., 2014). Lack of social support was also a risk factor in older adults for membership in a trajectory class characterized by higher symptoms (Byers et al., 2012; Hsu, 2012; Kuchibhatla et al., 2012), although somewhat surprisingly, marital status was not (Byers et al., 2012; Hsu, 2012; Montagnier et al., 2014). Once again there was a dose-response-like relationship between the majority of predictor variables and odds of membership in trajectory classes of escalating severity. For example, Byers et al. (2012) found that odds ratios for being in the persistently low, increasing, and persistently high trajectory classes relative to the minimal symptom class were 1.60, 2.09 and 2.41, respectively, for past history of myocardial infarction.

Among individuals with a clinical depression diagnosis, daily smoking and past history of depression were robust predictors of membership in a trajectory class characterized by recurrence (Colman et al, 2011) and past history of medical conditions, avoidance coping and lack of psychological flexibility predicted membership in a

trajectory class characterized by chronic high symptom burden (Cronkite et al., 2013). Among first-onset cases, predictors of recurrence included severity of symptoms at baseline and a history of migraine headaches (Colman et al., 2011).

Table 2.2: *Predictors of membership in a trajectory class characterized by higher symptom burden in children/adolescents*

Study	Problems with peers[a]	Problems with family[b]	Low Family income	Parent depression	Childhood Psychopathology[c]	Poor academic performance	Negative cognition[d]	Stressful /negative life events[e]	Alcohol Tobacco Drug use
Stoolmiller et al., 2005	-	√	√	√	√	√	-	√	-
Costello et al., 2008	√	√	√	-	√	-	√	-	√
Mazza et al., 2010	√	ns	√*	ns	√	ns	ns	ns	-
Chaiton et al., 2013	-	-	-	-	-	-	-	-	-
Duchesne et al., 2013	-	√	-	-	√	√	-	-	-
Yaroslavsky et al, 2013	√	-	-	√	√	-	√	√	√
Mezulis et al., 2014	-	-	-	-	-	-	√	-	-

'√' = the study examined the variable and found that it was significantly associated with a depression trajectory characterized by high symptom burden
'ns' = the study examined the variable and found that it was not significantly associated with a depression trajectory characterized by high symptom burden
'-' = the variable was not examined in that study

[a]Peer rejection, social competency, connection,
[b]Parental transitions, family conflict, connection, attachment to parents
[c]Anxiety, depression, attention problems, antisocial behavior, delinquent behavior
[d] low self-esteem, rumination, personal and cognitive coping
*significant in males only

Table 2.3: *Predictors of a membership in a trajectory class characterized by higher symptom burden in mothers*

Study	Younger Maternal Age	Lower Maternal education	Lower income	Marital instability/quality	Past history of depression	Difficult child*
Campbell et al., 2007	√	√	√	√	-	-
Gross et al., 2009	-	-	√	-	-	√
Luomo e al., 2015	ns	-	-	ns	√	-
Van der Waerden et al., 2015	-	ns	ns	-	√	-

'√' = the study examined the variable and found that it was significantly associated with a depression trajectory characterized by high symptom burden
'ns' = the study examined the variable and found that it was not significantly associated with a depression trajectory characterized by high symptom burden
'-' = the variable was not examined in that study

*includes behavioral and developmental difficulties

Table 2.4: *Predictors of membership in a trajectory class characterized by higher symptom burden in older adults*

Study	Chronic disease	Poor self-reported health	Tobacco smoking	Cognitive impairment	Functional impairment	Past depression	Low Social Support	Marital Status	Lower education	Lower Income
Liang et al., 2011	√	√	-	-	-	√	-	-	√	√
Kuo et al., 2011	√	√	-	ns	-	-	-	-	√	-
Hsu et al., 2011	√	-	-	-	√	√	√	ns	-	-
Byer et al., 2012	√	-	√	ns	√	-	√	ns	√	-
Kuchibhatla et al., 2012	-	√	-	√	√	-	√	-	√	-
Andreescu et al., 2007	-	-	-	√	√	√	-	-	√	-
Montagnier et al., 2014	√	-	ns	√	√	√	-	ns	√*	-

'√' = the study examined the variable and found that it was significantly associated with a depression trajectory characterized by high symptom burden
'ns' = the study examined the variable and found that it was not significantly associated with a depression trajectory characterized by high symptom burden
'-' = the variable was not examined in that study

*significant at the p = .06 level

Outcomes associated with trajectory class membership

Chaiton et al. (2013) looked at the effect of depression trajectories in adolescents on mental health in young adulthood and found that the rate of diagnosed mood or anxiety disorders was 3 times as high among girls and twice as high among boys who experienced a depression trajectory in adolescence characterized by high symptoms. Individuals in the high trajectory group were also more likely to have taken antidepressant medications in the past month and to report higher stress levels, and boys in the high depression trajectory group were more likely than boys in the moderate or low trajectory groups to have sought psychiatric care. Yaroslasky et al. (2013) looked at the impact of depression trajectories in adolescence on outcomes at age 30, including marital status, educational attainment, income, coping, dysfunctional attitudes, life events and daily hassles, self-esteem and social adjustment. They found that at age 30, individuals who were in the high or moderate depressive symptoms trajectory classes during adolescence were less well-adjusted overall than individuals in moderate or low trajectory groups. Specifically, they were less likely to be married (both more likely to be never married and more likely to be divorced), less likely to have a high school or a college degree, more likely to be lower or working class in terms of income, more likely to have dysfunctional attitudes, low self-esteem and poor coping skills and more likely to have experienced stressful life events and daily hassles. They also reported more episodes of major depression, anxiety and substance abuse relative to individuals in the low depression trajectory class. Salmela-Aro et al. (2008) looked at outcomes associated with depression trajectories in young adults. They found that individuals in the moderate and high depression trajectory classes in their 20s were less likely to have graduated from

college, had lower salaries, more symptoms of burnout, poorer quality of interaction with partners, lower achievement and self-efficacy and greater social avoidance in their early 30s relative to individuals in the low trajectory class.

Studies of depression trajectories in mothers found that maternal depression trajectories were associated with poor outcomes in their children. Both Campbell et al. (2007) and Matijasevich et al. (2015) found that maternal depression trajectories characterized by higher symptom burdens were associated with higher rates of internalizing behavior in children. Campbell et al. (2007) also found that moderate increasing and high decreasing trajectories were associated with poorer social skills and also, along with high-chronic symptom trajectories, with poorer cognitive skills relative to low and moderate stable depression trajectories, and that high-chronic trajectory in mothers was associated with lower competence in children relative to the low stable class. Gross et al. (2009) and Matijasevich et al. (2015) both found that maternal depression trajectories characterized by higher symptom burdens were associated with higher rates of externalizing behavior in offspring. Wickham et al. (2015) found that maternal depressive symptom trajectories, particularly trajectories with high symptoms during middle childhood, were associated with risky health behaviors in offspring such as smoking, alcohol and drug use.

Only two studies examined outcomes associated with depression trajectories in older adults. Kuo et al. (2011) examined differences in BMI, metabolic functions and cortisol by depression trajectory class at the end of a 10-year follow-up period and found that older adults who experienced persistent higher depressive symptoms had on average lower BMIs and higher levels of cortisol than older adults with low depressive symptom

trajectories. The authors found no differences in blood pressure, blood glucose or cholesterol between the different depression trajectory classes. Hybels et al. (2015) found that older adults with depression trajectories characterized by higher symptom burdens were more likely to experience oral health problems.

2.5 Discussion

Main findings

The goal of this chapter was to review studies that characterized heterogeneity in long-term (i.e. 5+ years) trajectories of depression using group-based trajectory models. We identified 26 studies of 25 separate samples that met criteria for inclusion in the review. Most of the studies focused on specific population groups such as adolescents, mothers and older adults. All but two of the studies looked at trajectories of depressive symptoms without reference to a clinical diagnosis of depression. The number of latent trajectory classes ranged from 2 to 6, with most of the studies identifying either 4 or 6 classes. Patterns of trajectories varied in terms of severity (mild, moderate, severe) and stability (stable, increasing, decreasing). Predictors of poor depressive symptom trajectory included female gender, low income (or in the case of children/adolescents, low parental income), low education (or in the case of children/adolescents, low academic achievement), past history of depression or other psychopathology, and stressful life events. Additional predictors of poor depression trajectories in adolescents included problems with peers and parents, alcohol/tobacco/drug use, parental history of depression and negative cognitive styles. Additional predictors of poor depression trajectories in mothers included younger maternal age, marital instability, past history of depression or anxiety and behavioral problems in the child. Additional predictors of poor

depression trajectory in older adults included poor self-rated health, past history of somatic illness, functional and cognitive impairment and low social support. Outcomes associated with poor depression trajectories included increased risk for diagnosed psychiatric disorders and use of antidepressant medications, lower income and educational attainment, lower probability of being married and lower self-esteem/self-efficacy. In mothers, poor depression trajectories were associated with poor social and behavioral outcomes in offspring. In older adults, poor depression trajectory predicted higher cortisol levels and poor oral health.

A comparison of depression trajectory patterns from the 26 studies included in this review yields several observations. First, stability of depressive symptoms over time appears to be more common than instability. Second, the majority of individuals either have no depressive symptoms or minimal depressive symptoms over time. Third, experiencing a trajectory that includes moderate depressive symptoms, even chronic moderate symptoms, appears to be fairly common, particularly among adolescents, but a trajectory characterized by high depressive symptoms is rare. Nevertheless, a small proportion (< 10%) of individuals across different populations and even age groups persistently demonstrated chronic, high levels of depressive symptoms for extended periods of time. Individuals following this type of trajectory pattern were more likely to be diagnosed with depression or anxiety disorders, which suggests that individuals with this type of trajectory either suffer from clinical depression already, or will do so in the future. Either way, from a clinical perspective, this group of individuals is highly important and warrants further attention and study.

The studies in this review revealed consistent differences in long-term depression trajectories based on gender, age and race. Although not associated with differences in trajectory patterns, female gender was a robust predictor of membership in a trajectory class characterized by higher depressive symptoms. This is consistent with the finding that depression is more common in females than in males (Weissman & Klerman, 1985), as well as the finding that female gender is a risk factor for recurrence among individuals diagnosed with clinical depression (Kessing, Andersen, & Mortensen, 1998; Mueller et al., 1999). High symptom trajectories contained larger proportions of the sample in studies conducted in adolescents compared to studies conducted in adults and older adults, which is consistent with previous evidence that depression symptoms are highest among adolescents (Garber, Keiley, & Martin, 2002; Sutin et al., 2013). Finally, several studies found that non-white race was associated with membership in a trajectory class with higher symptoms. This may be driven at least in part by correlations between race and other demographic variables associated with depression trajectory, including education and income. It may also reflect higher levels of stress due to discrimination faced by many individuals in non-white racial groups.

It is unclear from the existing studies whether many of the identified associations between antecedents/outcomes and depression trajectories are necessarily causal or, if they are causal, what the direction of causality might be. For example, Gross et al. (2009) showed that a high depression trajectory in mothers was associated with later externalizing and antisocial behaviors in children, but it is unclear whether the children were acting out in response to their mother's depression, whether the mothers experienced more depressive symptoms because their children were badly behaved, or

whether both maternal depression and child externalizing/antisocial behavior were in fact caused by some third variable. Similarly, Liang et al. (2012) showed that the number of chronic diseases reported by older adults at baseline was associated with higher depressive symptom trajectories during follow-up, but since individuals with previous depressive symptoms were included in the analysis, it is impossible to determine whether the somatic illness led to higher depressive symptom trajectories or whether previous depressive symptoms led to both increased incidence of somatic illness and higher depressive symptom trajectories during the period of follow-up.

Directions for future research

Previous studies have alluded to heterogeneity in course trajectories of MDD: Eaton et al. (2008) examined the long-term course of depression in 92 incident community cases in the Epidemiological Catchment Area (ECA) follow-up and found that 50% of MDD cases experienced only a single episode, 35% experienced a remitting and recurring course, and 15% of cases experienced chronic MDD symptoms. Similarly, Angst et al. (2009) assessed the cumulative incidence of chronic depression and episodic depression in the Zurich Cohort Study and found that the cumulative incidence of chronic depression was 6%, while the cumulative incidence of episodic MDD was 21%. Only two of the studies included in this review evaluated trajectories of depression among clinical depression cases, and these studies had relatively small sample sizes (for group-based trajectory models) and assessed participants at only 4-5 time points. Future studies with larger samples and more frequent, consistent assessments of depression status are needed in order to shed light on heterogeneity in long-term depression trajectories among individuals with a diagnosis of MDD.

Another potential avenue for future studies is to untangle the web of causation relating depression trajectories to predictors and outcomes. To accomplish this, studies must first establish temporal associations between predictor and outcome variables and the start or end of the trajectory. This endeavor will be more straightforward, particularly for predictor variables, when modeling trajectories of course, as course trajectories are temporally bounded in a way that symptom trajectories in non-clinical samples are not.

Methodological considerations

Group-based trajectory models require large sample sizes in order to accurately and precisely estimate trajectories for multiple classes, particularly when the proportion of individuals falling within a given class is small. This review was limited to studies with at least 200 people in the sample, but many of the studies far exceeded this requirement: 73% (19 out of 26) of the studies had samples sizes greater than 500 individuals, and 58% (15 out of 26) had samples greater than 1,000 individuals. Similarly, although the inclusion criteria specified that the time-frame of follow-up be at least 5 years, many of the studies far exceeded this as well: 65% (17 out of 26) followed participants for 10 or more years.

Despite the large sample sizes and lengthy durations of follow-up, many of the studies assessed depression in participants using at only a few time points. Three time points is the bare minimum required to estimate a quadratic trajectory, however additional time points are often needed in order to estimate trajectories with cubic or quartic shapes (Andruff, Carraro, Thompson, Gaudreau, & Louvet, 2009). The finding that stability in depressive symptoms over time was more common than instability must be interpreted with caution in light of this fact, as these studies may have had insufficient

data to estimate more complex trajectory patterns. An additional limitation of many of these studies is the fact that they used shortened forms of established depressive symptom measures. Depression was measured with as few as 3-6 items at each time point in some studies, which brings the validity of their assessments of depression measures into question.

Limitations

The greatest limitation of this review is the fact that it relies solely on qualitative comparisons of studies. To our knowledge, there is no quantitative method currently in existence to combine results from multiple group-based trajectory models, short of combining the individual samples themselves. As a result, it was impossible to account quantitatively for differences in the methodological quality of the studies. A second limitation of this review is that studies were identified, extracted and compared by a single person, the first author.

Conclusions

Most of the studies using group-based trajectory models to characterize heterogeneity in long-term trajectories of depression identify either 4 or 6 distinct trajectory classes. Patterns of depression trajectories vary in terms of severity (mild, moderate, severe) and stability (stable, increasing, decreasing). Overall, stable depressive symptoms over time appear to be more common than unstable depressive symptoms, regardless of severity. Most people follow a trajectory characterized by minimal depressive symptoms, but a notable minority (somewhere between 2 and 15%) experience persistent high depressive symptoms over long periods of time. Predictors of membership in a trajectory class characterized by higher depressive symptoms include

female gender, younger age, low income/education, non-white race, and stressful life events. Trajectories characterized by high symptoms are associated with poor psychiatric and psychosocial outcomes.

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CHAPTER 3: Heterogeneity in 10-year course trajectories of MDD

3.1 Abstract

Objective: To characterize patterns and predictors of 10-year course trajectories of major depressive disorder (MDD) in a population-representative sample.

Method: Data was obtained from Danish civil and psychiatric national registers. The sample contained 14,564 MDD cases with age of onset < 60, first admitted with MDD between 1995 and 2002. Individuals ever diagnosed with bipolar or schizophrenia-spectrum disorders were excluded. The primary response variable was the log odds of past-year inpatient or outpatient MDD treatment during the 10-year period following the first MDD diagnosis. Predictor variables included demographic characteristics, characteristics of the first MDD episode and parental history of psychiatric diagnoses. Trajectories were modeled using latent class growth analysis.

Results: The optimal model contained four classes: An *early recovery* class (class 1; 72.2%), a *prolonged initial illness* class (class 2; 16.1%), a *later recurrence* class (class 3; 8.1%) and a *chronic illness* class (class 4; 3.6%). Female gender, inpatient treatment, and severity of the initial MDD episode were associated with increased odds of a more severe trajectory (classes 2, 3, 4) relative to class 1. Past history of suicide attempt/self-harm was associated with membership in the later recurrence class. Parental anxiety and depression predicted membership in the later recurrence class and parental psychotic illness predicted membership in the chronic illness class.

Conclusions: Most people treated for MDD in Danish psychiatric facilities have good 10-year prognoses. A large proportion of specialized MDD treatment in Denmark goes to a minority of patients. The fact that different parental disorders predicted different course trajectories suggests that observable heterogeneity in course may be indicative of differential underlying etiologies.

Keywords: major depressive disorder, course trajectories, parental history, registry-based research

3.2 Introduction

There is a large amount of heterogeneity in patterns of illness course among individuals diagnosed with major depressive disorder (MDD). Results from the Epidemiological Catchment Area (ECA) study follow-up suggest that 50% of individuals who experience an MDD episode do not experience another episode, 35% experience a course characterized by recovery and subsequent recurrence, and 15% experience chronic MDD symptoms (Eaton et al., 2008). Results from the Collaborative Depression Study, a longitudinal study of clinical MDD patients, suggest that while the majority of MDD patients recover from an episode within 1 year, 12% of patients have not recovered after 5 years and 6% have not recovered even after 15 years (Boland & Keller, 2009).

Characterizing the heterogeneity in long-term MDD course trajectories is important for several reasons. First, individuals with different course trajectories likely have different treatment needs. Second, differences in patterns of long-term course may be indicative of underlying differences in etiology. Finally, phenotypic heterogeneity has been cited as one of the primary reasons for lack of genetic findings in MDD (Levinson et al., 2014). Parsing the heterogeneity in depression course and identifying predictors of different course trajectories has the potential to change how we understand and treat depression, and ultimately could improve our ability to intervene effectively and rationally to prevent or mitigate this disorder.

Characterizing long-term course trajectory patterns, particularly rare ones, is difficult because it requires longitudinal data on large numbers of cases collected over long periods of time. The Danish Psychiatric Central Register (Mors, Perto, & Mortensen, 2011) contains decades of information on the psychiatric history of the entire

population of Denmark, and as such provides a rare opportunity to examine long-term trajectories in a large, nationally representative sample. Our goal in this study was to use data from the Danish civil and psychiatric registers to model latent trajectories of MDD inpatient and outpatient admissions during the 10-year period following first diagnosis, and to examine predictors of course trajectory class membership.

3.3 Method

Data Sources: The Danish Population Registers

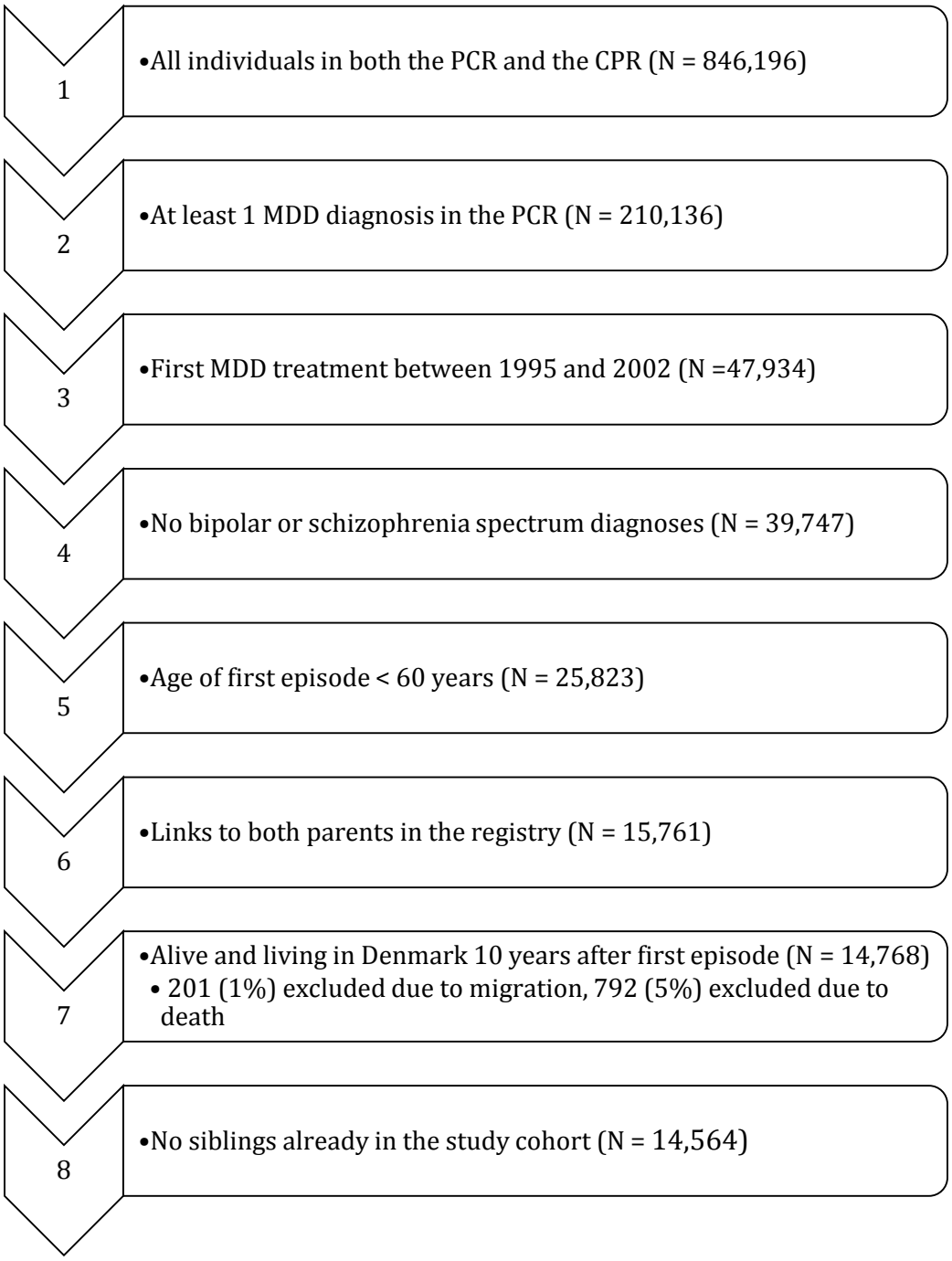
The Danish registry system includes multiple registers that continuously record, store and update information on the entire population of Denmark. Information from different registers can be linked using the personal identification (CPR) number. Demographic variables including gender, date of birth, place of birth and links to parents may be obtained from the Danish Civil Register (Pedersen, 2011). Information on psychiatric disorders, including MDD, is available in the Psychiatric Central Research Register (PCR; (Mors et al., 2011)). This register contains the start and end dates of treatment, as well as diagnoses, for all inpatient hospitalizations for psychiatric illness in Denmark since 1970 and all outpatient psychiatric treatment since 1995. Diagnoses are based on the International Classification of Diseases 8th edition (ICD-8) from 1970 to 1993 and on the International Classification of Diseases 10th edition (ICD-10) from 1994 onward.

Study Sample

Individuals were included in the study sample if they met the following criteria: first, they had to have at least one main diagnosis of MDD recorded in the PCR (See Appendix A for relevant ICD-8 and ICD-10 diagnostic codes). Second, they had to have

received their first MDD diagnosis between 1995 and 2002. This time frame was chosen because 1995 was the first year during which outpatient psychiatric visits were included in the registry and 2002 was the last year for which we could be certain of having 10 years of complete follow-up for all participants. Third, they could not at any point have received a bipolar or schizophrenia spectrum diagnosis (See Appendix B for exclusionary diagnostic codes) (Pedersen et al., 2014). This criterion was put in place to exclude individuals for whom the unipolar depression diagnosis was either inaccurate and later revised, or better characterized as a preliminary stage of a different psychiatric illness. Fourth, we restricted the sample to individuals who were alive and living in Denmark at least 10 years after their first MDD diagnosis. We chose not to include individuals with incomplete follow-up data in the analyses because an examination of missing data patterns suggested that the data was MNAR (Little & Rubin, 2002). Fifth, we included only individuals with links to both parents in the registry so that we could assess the associations between parental history of psychiatric diagnoses and course trajectory class membership. Sixth, we excluded individuals with a full or half-sibling already in the sample, as group-based trajectory models assume individuals are independent. Finally, we restricted the sample to individuals who were < 60 years old at their first diagnosis. This decision was made both for substantive and practical reasons. From a substantive perspective, literature suggests that late-onset depression may be etiologically different from earlier onset depression (Alexopoulos et al., 1997). From a practical standpoint, individuals with an age of MDD onset > 60 were far less likely to have links to parents in the registry. Figure 3.1 illustrates the pipeline used to select the study sample. The final sample contained 14,564 individuals.

Figure 3.1: *Sample Selection Pipeline*



Statistical Analysis

Course trajectories were modeled using latent class growth analyses (LCGA). LCGA is a group-based trajectory modeling technique in which trajectories are estimated separately for latent subgroups in a sample using information from an observed variable measured repeatedly over time (Jung & Wickrama, 2008; Muthen, 2004; Nagin, 1999). LCGA has been used to examine heterogeneity in depressive symptom trajectories in non-clinical samples of children (Mazza, Fleming, Abbott, Haggerty, & Catalano, 2010), adolescents (Costello, Swendsen, Rose, & Dierker, 2008), adults (Melchior et al., 2013), mothers (Cents et al., 2013), older adults (Liang, Xu, Quiñones, Bennett, & Ye, 2011; Taylor, Ezell, Kuchibhatla, Østbye, & Clipp, 2008) and somatic patients (Kuchibhatla & Fillenbaum, 2011). LCGA assumes there is no variation in course trajectory within each latent class (i.e. no random effects). The parameters of an LCGA model include the probability of membership in a particular latent trajectory class (η_j) for each individual as well as the intercept (π_{0j}) and slope (π_{1j}) of the trajectory for each class. LCGA models were estimated using PROC TRAJ (Jones, Nagin, & Roeder, 2001; Jones & Nagin, 2007) in SAS 9.4 (SAS Institute Inc., Cary, NC, USA) with a binary logit distribution. PROC TRAJ uses maximum likelihood to estimate model parameters.

Model fitting and selection process

The primary response variable was the log odds of specialized psychiatric treatment (in either an inpatient or outpatient setting) for MDD each year during the 10-year period following an individual's first MDD diagnosis. To determine the optimal number of groups we fit models with between 1 and 7 latent trajectory classes. Quartic polynomial terms were specified for trajectory slopes in all models except for the 5 and 6

class models, which experienced convergence or multi-collinearity problems with quartic terms and were therefore run with cubic terms. If a polynomial function term for a given class was not statistically significant, we ran the model without it and if the resulting model had a lower BIC than the model with up to quartic terms, we used the later model for comparison with models containing different numbers of classes. Trajectory patterns for the resulting models are shown in Figures 3.2-3.8.

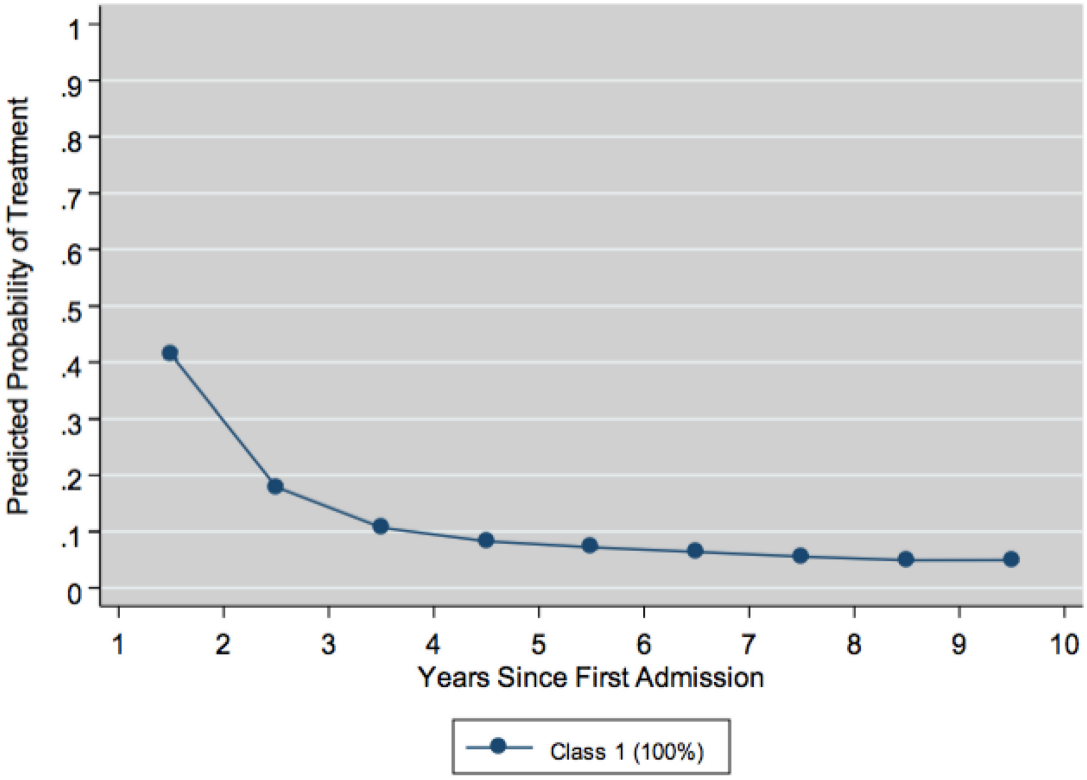
The final model was chosen based on three factors: a) model fit statistics, with weight placed on BIC values (Nylund, Asparouhov, & Muthén, 2007), b) average posterior probabilities of class membership (Nagin, 1999) and c) clinical utility. A comparison of BIC values (Table 3.1) suggested that the 7-class model was the best fit for the data, and that we might even have considered adding more latent classes. Examination of the log bayes factor, which indicates the extent to which a model with *j* classes represents a significant improvement over a model with *j*-1 classes, suggested that the 6-class model was the best fit for the data. We were wary of placing too much emphasis on goodness-of-fit statistics for model selection however, as LCGA does not allow for within-class variation and therefore fit statistics may overestimate the number of latent classes. We also examined scree-like plots of the AIC and BIC values for the 7 models (Giang & Graham, 2008; Lanza, Huang, Murphy, & Hser, 2013). As shown in Figures 3.9 and 3.10, the elbow of the scree-plots was at the 2-class model, and at the 4-class model the improvement in model fit leveled off entirely.

Table 3.2 shows the average posterior probability of class membership in each class for each of the 7 LCGA models. Posterior probability of class membership is the probability that an individual belongs to a given class based on his or her response

pattern. Proc Traj assigns individuals to the class to which they have the highest probability of belonging. Average maximum posterior probability is therefore an indicator of the precision with which the model classifies individuals into different classes based on their response patterns. Models with up to 5 classes had average posterior probabilities of class membership above .80 for all classes, which is considered highly adequate (Andruff, Carraro, Thompson, Gaudreau, & Louvet, 2009).

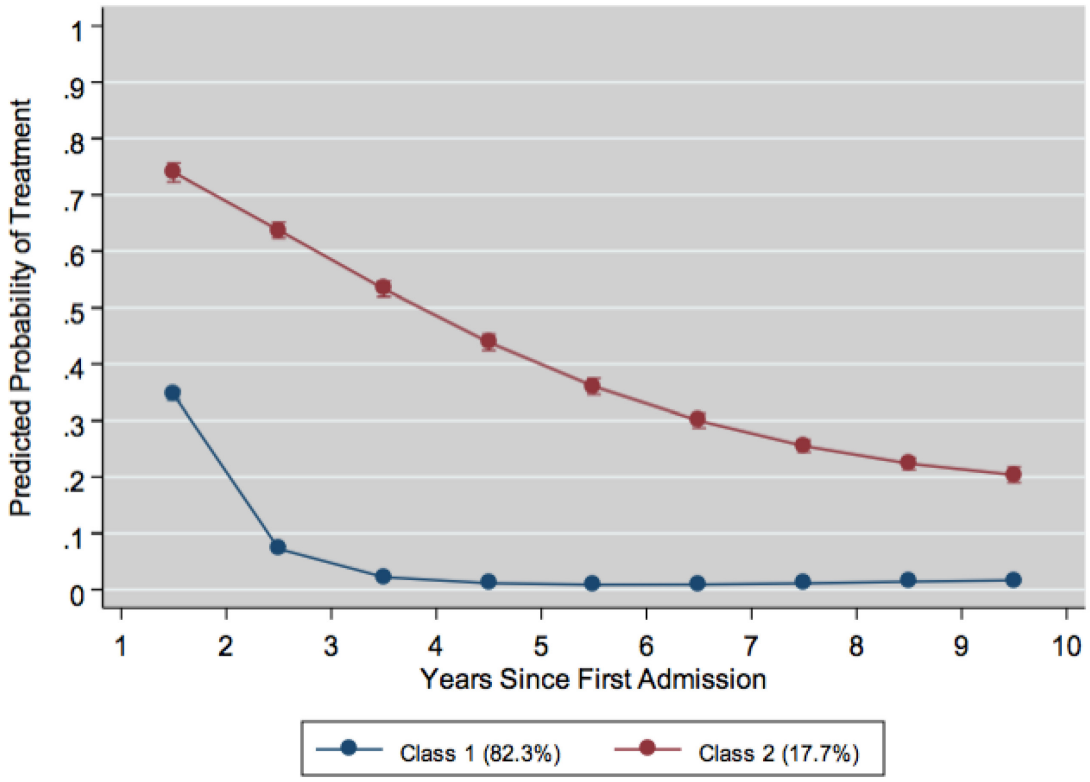
We selected the 4-class model because it represented the best choice in terms of all three of our criteria for model selection. Models with additional latent classes did have better BIC values, but improvement in BIC was negligible after 4-classes. Additionally, many of the added classes contained very small proportions of the sample (1-2%) and appeared to be minor variations on trajectory patterns already represented in the 4-class model. The 4-class model demonstrated satisfactory precision (i.e. average posterior probability of class membership > 80%). An examination of residual variation in treatment within classes (see Appendix C for a visual representation of individual-level data patterns), confirmed that the 4-class solution identified distinct trajectory patterns while allowing for individual variation within classes.

Figure 3.2: *10-Year course trajectories of early-onset MDD: 1 class model*



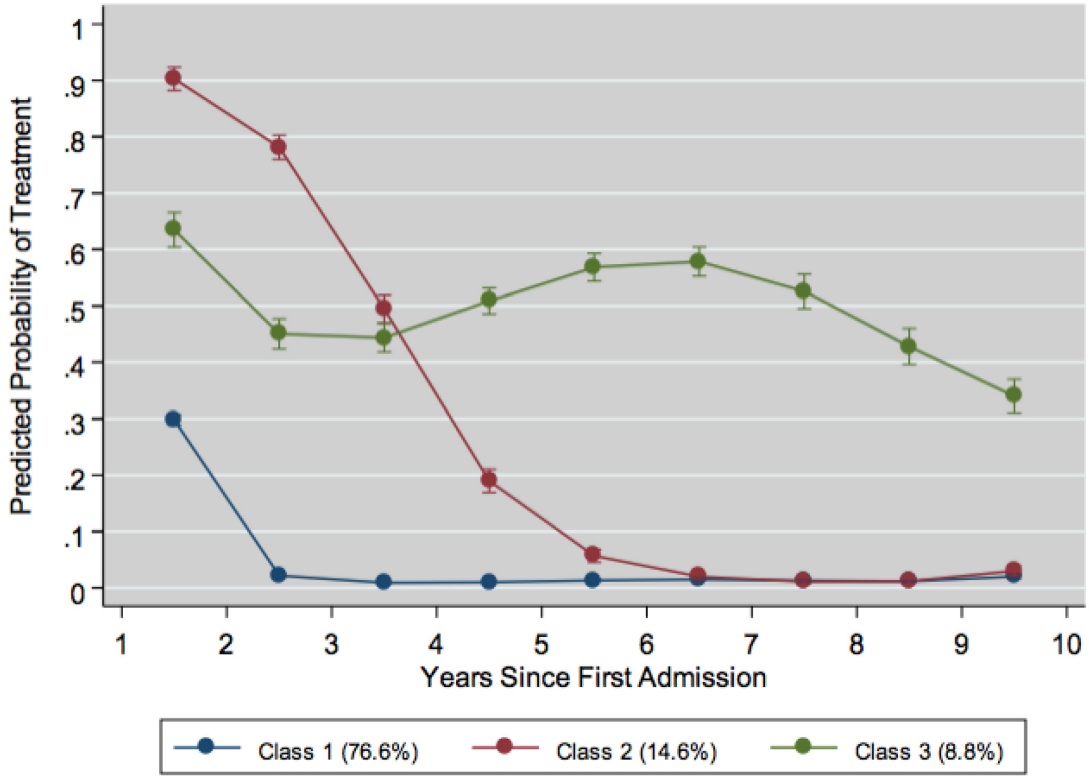
Note. Bars represent 95% confidence intervals.

Figure 3.3: *10-Year course trajectories of early-onset MDD: 2 class model*



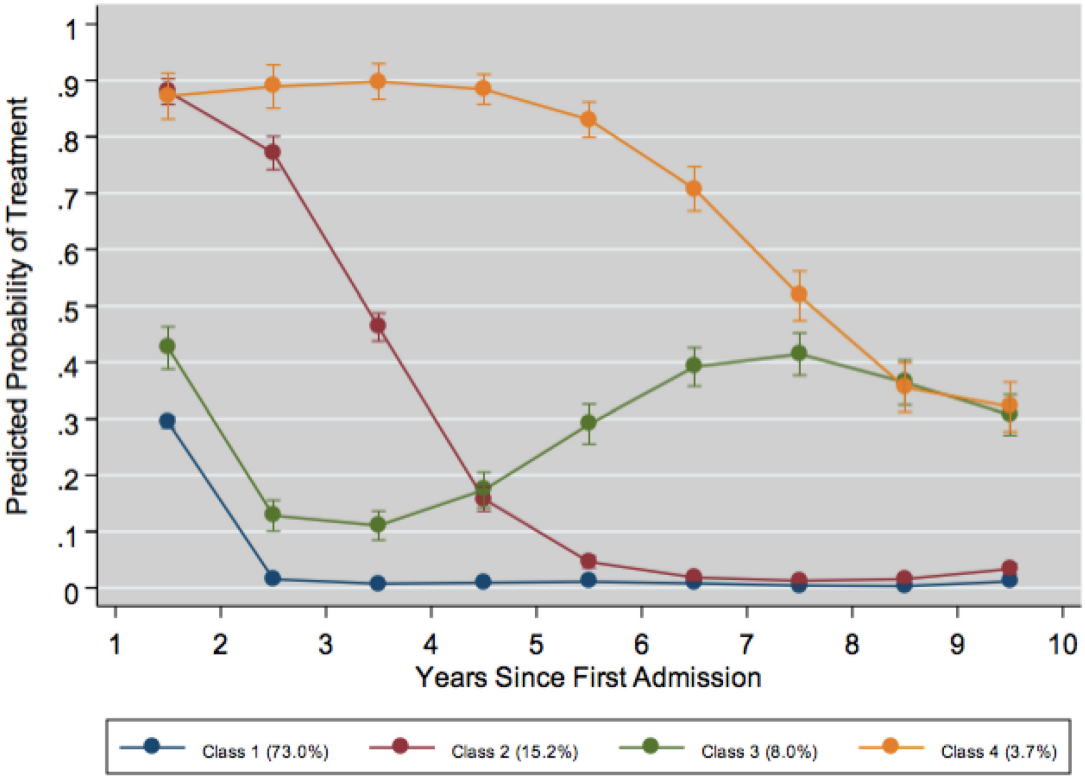
Note. Bars represent 95% confidence intervals.

Figure3.4: *10-Year course trajectories of early-onset MDD: 3 class model*



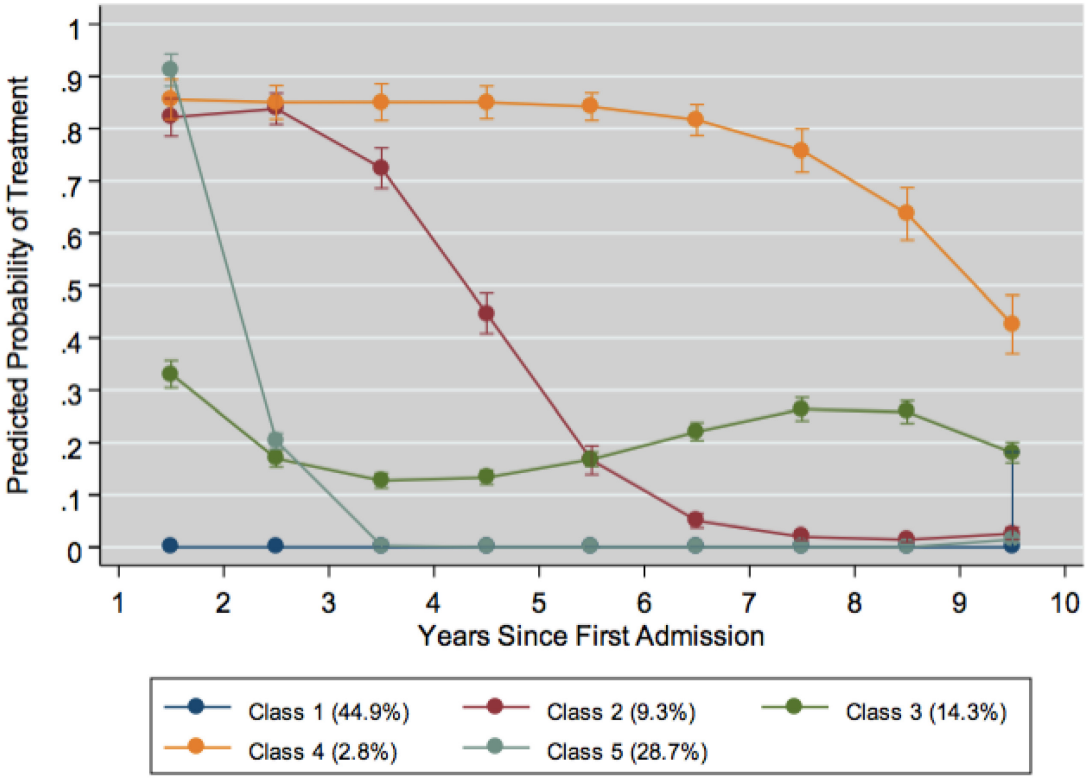
Note. Bars represent 95% confidence intervals.

Figure 3.5: *10-Year course trajectories of early-onset MDD: 4 class model*



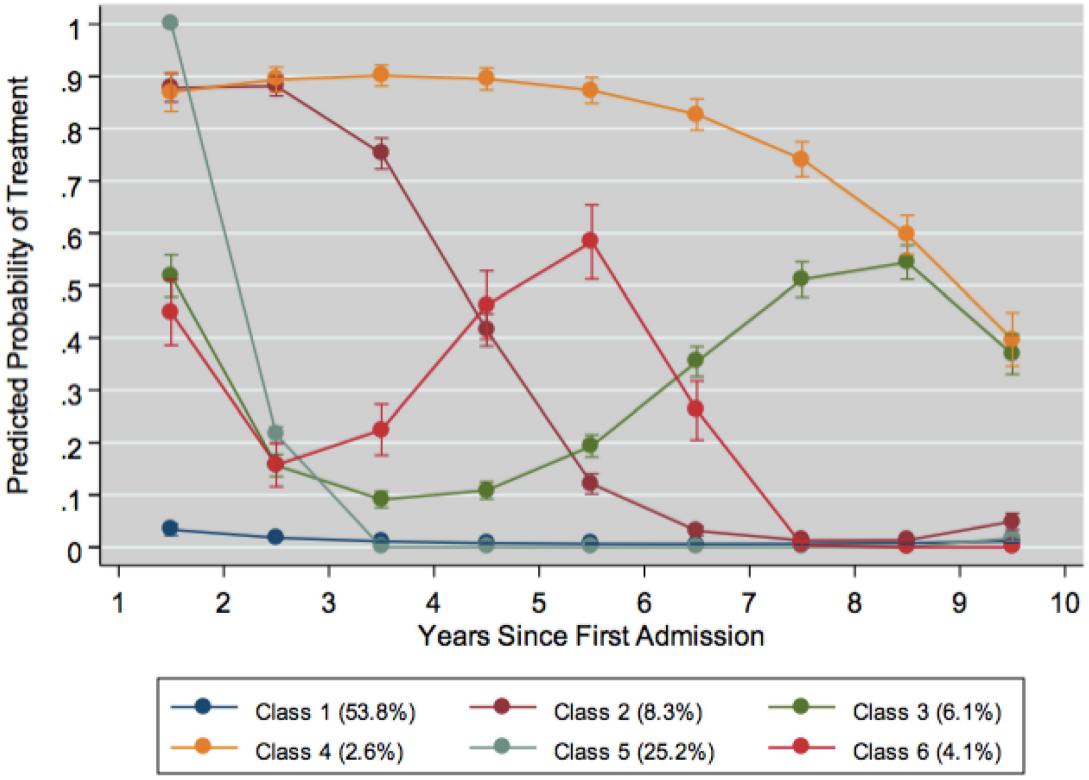
Note. Bars represent 95% confidence intervals.

Figure 3.6: *10-Year course trajectories of early-onset MDD: 5 class model*



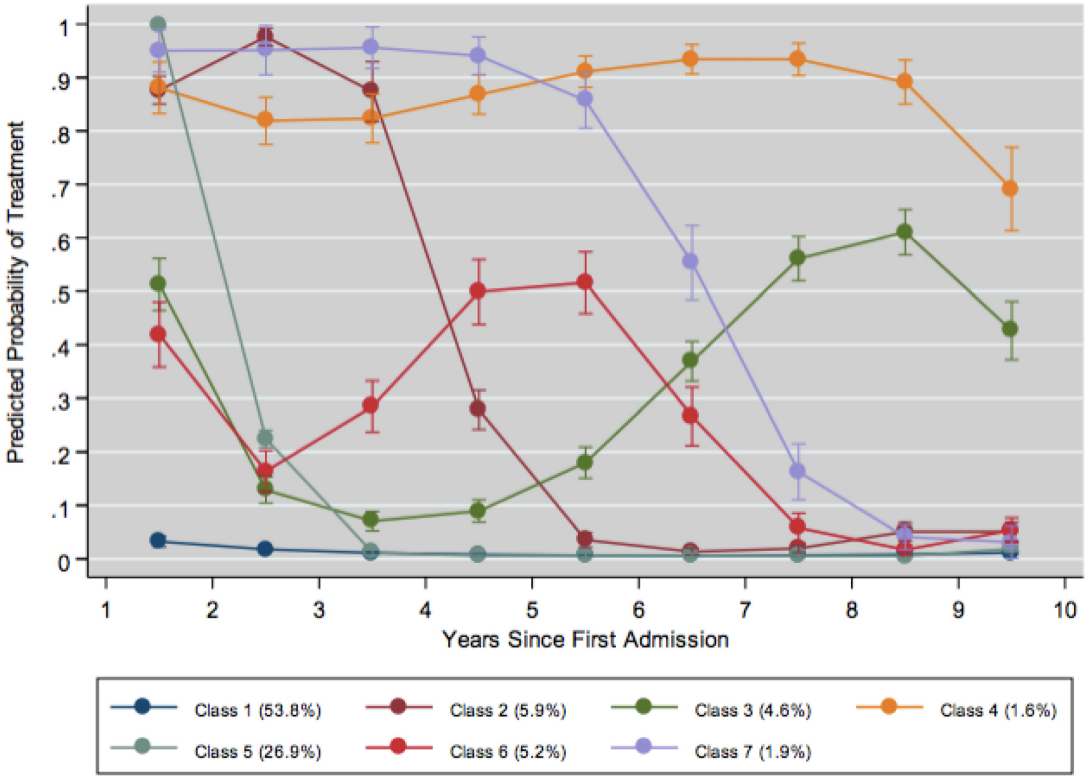
Note. Bars represent 95% confidence intervals.

Figure 3.7: *10-Year course trajectories of early-onset MDD: 6 class model*



Note. Bars represent 95% confidence intervals.

Figure 3.8: *10-Year course trajectories of early-onset MDD: 7 class model*



Note. Bars represent 95% confidence intervals.

Table 3.1: *Comparison of fit statistics for models with between 1 and 7 classes*

No. of Classes	AIC	BIC	Null Model	ΔBIC	Log Bayes Factor
1	-41922.44	-41941.41	-	-	-
2	-36057.92	-36088.27	1 Class	5853.14	11706.28
3	-34670.13	-34730.82	2 Classes	1357.45	2714.9
4	-33984.87	-34072.12	3 Classes	658.7	1317.4
5	-33911.72	-34002.76	4 Classes	69.36	138.72
6	-33474.37	-33576.78	5 Classes	425.98	851.96
7	-33210.74	-33351.09	6 Classes	225.69	451.38

Table 3.2*: Average posterior probability of class membership for models with 1-7 classes*

	Number of Latent Classes In Model													
	1		**2**		**3**		**4**		**5**		**6**		**7**	
Class	%	APP	%	APP	%	APP	%	APP	%	APP	%	APP	%	APP
1	100	1.0	82.3	0.97	76.6	0.97	73.0	0.95	44.9	0.92	53.8	0.97	53.8	0.97
2	-		17.7	0.94	14.6	0.88	15.2	0.91	9.3	0.91	8.3	0.92	5.9	0.92
3	-		-		8.8	0.89	8.0	0.83	14.3	0.92	6.1	0.89	4.6	0.84
4	-		-		-		3.7	0.89	2.8	0.89	2.6	0.92	1.6	0.94
5	-		-		-		-		28.7	0.91	25.2	0.89	26.9	0.90
6	-		-		-		-		-		4.1	0.74	5.2	0.78
7	-		-		-		-		-		-		1.9	0.85

% = percent of the population assigned to that class. APP = average posterior probability of group assignment within that class.

Figure 3.9: *Scree-like plot of -AIC values for models with 1-7 classes*

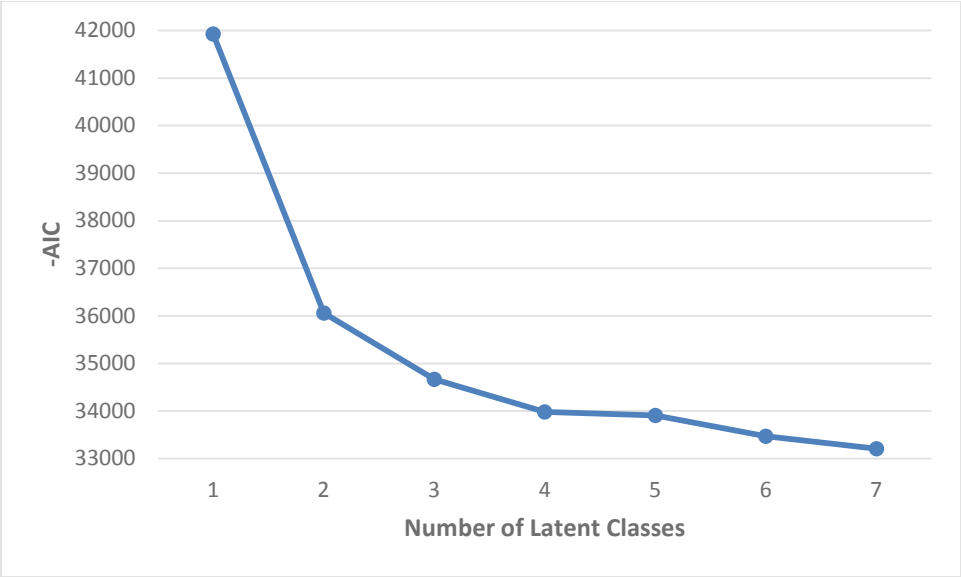
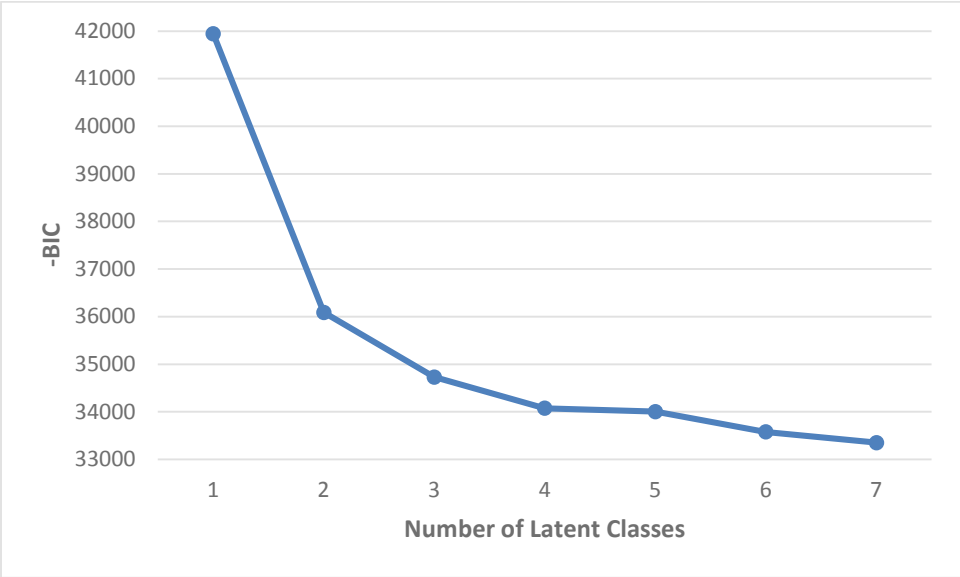


Figure 3.10: *Scree-like plot of -BIC for models with 1-7 classes*



Predictors

We examined the following predictors of course trajectory class membership: demographic characteristics (gender (male/female), place of birth (urban, rural, other) and birth year), characteristics of the first episode (calendar year of initial diagnosis, age at initial diagnosis, inpatient treatment at initial diagnosis, whether initial treatment occurred in an inpatient setting, past history of suicide attempt/self-harm, severity of symptoms at first diagnosis (mild, moderate, severe without psychotic features, severe with psychotic features) and parental history of psychiatric diagnoses (unipolar depression, bipolar disorder, psychotic illness, substance abuse and anxiety disorders). Table 3.3 lists the ICD diagnostic codes and categories used to define psychiatric illness in parents.

We began by examining predictors descriptively, assigning individuals in the study sample to their most likely trajectory class and comparing frequencies of predictor variables across classes. Next, we examined the odds of membership in different trajectory classes by re-fitting the 4-class LCGA model with predictor variables – the so called "one-step approach" (Vermunt, 2010). The benefit of this approach (fitting the measurement and structural components of the LCGA model simultaneously) as opposed to performing a standard multinomial logistic regression analysis with trajectory class membership as the outcome is that it accounts for uncertainty in trajectory class assignment (Nagin, 1999). We fit separate models for each predictor, but as the coefficients from these models were similar to those from a single model including all predictor variables, we report results of the combined model only. Although all slope parameters (linear, quadratic, cubic, quartic) in the unconditional 4-class model were

statistically significant, after adding predictor variables the model demonstrated greater parsimony and lower BIC by removing the cubic and quartic terms from class 2.

Sensitivity Analyses

We conducted several sensitivity analyses to evaluate the robustness of the trajectory patterns to variations in our sampling procedures. First, we ran the model in a sample of MDD cases that included individuals who were at some point diagnosed with bipolar disorder or a schizophrenia-spectrum disorder (N = 18,418) to determine how representative the trajectories were of MDD course trajectories in all individuals who receive an MDD diagnosis. Second, we ran the model among only those in the study sample born in 1980 or later (N = 1,774). Because the registry only began recording outpatient treatment in 1995, some older individuals in the cohort may have had an unrecorded history of outpatient treatment. Thus, the first diagnosis recorded in the registry may not always represent the first episode of MDD. Individuals born in 1980 or later were 15 years old in 1995 (the beginning of the inclusion window) and therefore the most likely to be truly incident cases.

Table 3.3: *ICD-8 and ICD-10 diagnostic codes used to characterize parental history of psychiatric diagnoses*

Disorder category	ICD Code	Diagnosis
Unipolar depression	296.0	Involutional melancholia
	296.2	Manic depression psychosis, depressed type
	298.0	Reactive depression psychosis
	300.4	Depressive neurosis
	F32	Depressive episode
	F33	Recurrent depressive disorder
Bipolar disorder	296.1	Manic depressive psychosis, manic type
	296.3	Manic depressive psychosis, circular type
	298.1	Reactive excitation
	F30	Manic episode
	F31	Bipolar disorder
Psychotic Illness	F20/295*	Schizophrenia
	F21	Schizotypal disorder
	F22	Persistent delusional disorder
	F23	Acute and transient psychotic disorder
	F28/F29	Other/unspecified non-organic psychosis
Substance abuse	303/F10	Alcoholism
	304/F11-F19**	drug dependence
Anxiety disorder	300.0	anxiety neurosis
	300.2	Phobic neurosis
	300.3/F42	Obsessive compulsive disorder
	F40	Agoraphobia
	F40.1	Social phobia
	F40.2	Specific phobia
	F40.8/40.9	Other/unspecified phobia
	F41.1	Generalized anxiety disorder
	F43.1	Post-traumatic stress disorder

*Excludes 295.7: schizoaffective disorder
**Excludes F17, tobacco dependence

3.4 Results

Sample characteristics

Characteristics of the study sample are in Table 3.4. The sample was 63.7% female with a mean age at first MDD diagnosis of 32 years (*SD* = 9.6). Twenty-six percent received treatment for their first MDD episode in an inpatient setting, 12.9% had a past history of suicide attempt/self-harm, and 15.2% had severe symptoms with or without psychotic features (e.g. delusions, hallucinations, stupor) at their first diagnosis. Individuals in the sample were born between 1935 and 1994, and the age at first MDD admission ranged from 7-59 years.

Patterns of course trajectories

Parameter estimates for the 4-class model, including predictor variables, are shown in Table 3.5. Figure 3.11 shows the probabilities of treatment (inpatient or outpatient) each year for the 10-year follow-up period in each of the 4 course trajectory groups. The largest class, class 1, contained 72.2% of the sample and was characterized by *early recovery*. Individuals in this class had a 28% probability of either being continuously or intermittently in treatment between the first and second years following their first MDD diagnosis and a 1% probability for the remainder of the 10-year follow-up period. Class 2 (16.1% of the sample) was characterized by *prolonged initial illness.* The probability of admission/treatment for individuals in this class was high (91%) between the first and second year after initial diagnosis and then declined steadily across the first 5 years of follow-up. Similar to class 1, individuals in class 2 had ~2% probability of treatment during the second half of follow-up. Class 3 (8.1%) was characterized by *later recurrence.* These individuals began with a 41% probability of

treatment between the first and second years after initial diagnosis, which decreased to 10-20% and then increased back to 40% in the second half of the follow-up period. The smallest class, class 4 (3.6%) was characterized by *chronic illness*. These individuals had a high probability of admission/treatment (80-90%) throughout the first two thirds of the follow-up period, and a moderate-decreasing probability (30-40%) thereafter.

Predictors of course trajectory class membership

Frequencies of predictor variables by course trajectory class are shown in Table 3.6. Odds ratios and 95% confidence intervals from the LCGA model including covariates are shown in Table 3.7.

Demographic predictors. Female gender was associated with membership in the prolonged initial illness (OR = 1.74), later recurrence (OR = 1.46) and chronic illness (OR = 1.85) classes relative to the early recovery class. Later birth year was most strongly associated with membership in the prolonged initial illness group relative to the other classes (early recovery: OR = 1.78; later recurrence: OR = 1.44; chronic illness: OR = 1.18). Rural birthplace was associated with membership in the prolonged initial illness (OR = 1.32) and chronic illness (OR = 1.34) classes relative to the early recovery class.

Characteristics of the first admission. As calendar year of first admission increased, so did odds of membership in a class characterized by shorter treatment periods, indicating a possible secular trend. In contrast, higher age at first diagnosis was associated with membership in classes with more prolonged periods of treatment, especially the prolonged initial illness group. Inpatient treatment at initial diagnosis was associated with membership in the prolonged initial illness (OR = 1.30) and later recurrence (OR = 1.49) groups relative to the early recovery group. Past history of

suicide attempt/self-harm was associated with a trajectory characterized by shorter treatment periods, particularly the later recurrence group (early recovery: OR = 1.26; prolonged initial illness: OR = 1.92; chronic illness: OR = 1.89).

There was a dose-response-like relationship between severity of the initial episode (mild, moderate, severe without psychotic features, severe with psychotic features) and membership in more severe course trajectory classes relative to the early recovery class. One exception to the dose-response pattern was the later recurrence vs. early recovery group, in which the effect for psychotic symptoms (OR = 1.82) was smaller than that of severe symptoms without psychotic features (OR = 2.04).

Parental history of psychiatric disorders. Parental history of unipolar depression and anxiety increased the odds of being in the later recurrence group relative to the early recovery group (depression: OR = 1.46, anxiety: 1.33) and, with marginal significance, the prolonged initial illness group (depression: OR = 1.26, p = .08; anxiety: OR = 1.38, p = .06). Parental history of psychotic illness was significantly associated with membership in the chronic illness group relative to the early recovery group (OR = 2.06) and the later recurrence group (OR = 2.03) and, with marginal significance, the prolonged initial illness group (OR = 1.67, p = .09).

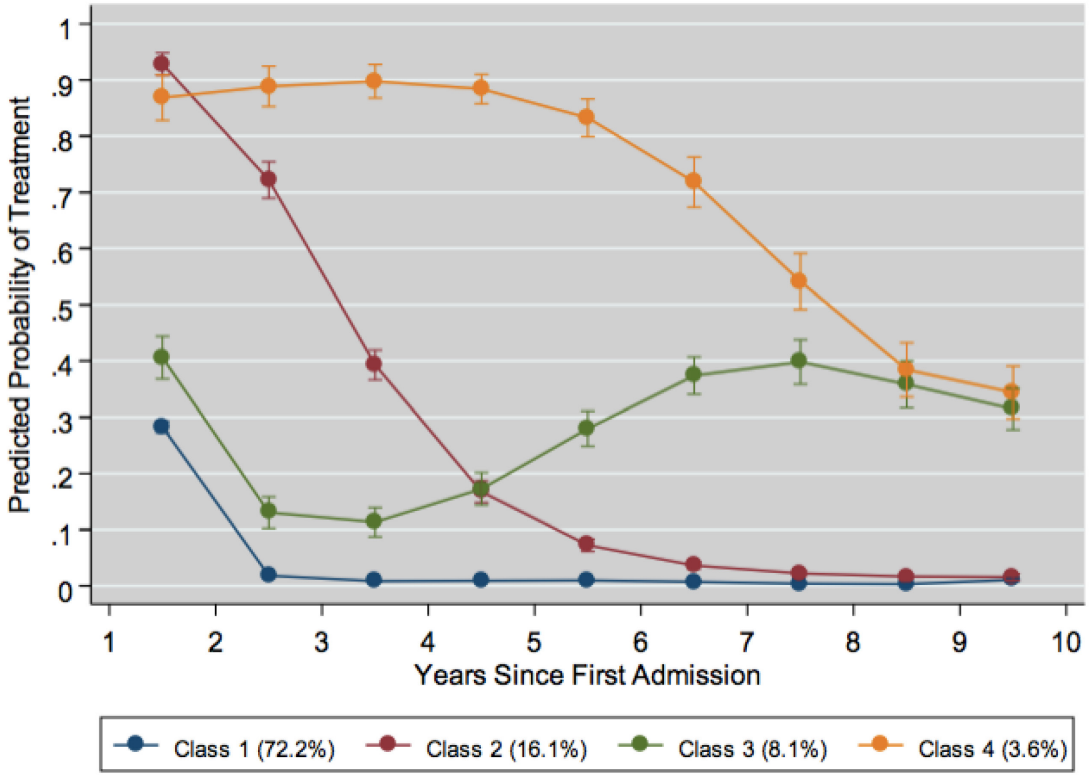
Table 3.4: *Characteristics of the study sample*

Characteristic	N (%)
Demographic characteristics:	
Gender (% female)	9,279 (63.7%)
Birthplace:	
Urban	10,610 (72.9%)
Rural	3,404 (23.4%)
Other	550 (3.8%)
Characteristics of 1st Admission:	
Age at first admission (M, SD)	32 (9.6) years
Calendar year:	
1995	900 (6.2%)
1996	1,046 (7.2%)
1997	1,347 (9.3%)
1998	1,565 (10.8%)
1999	1,910 13.1%)
2000	2,177 (15.0%)
2001	2,704 (18.6%)
2002	2,915 (20.0%)
Inpatient treatment	3,743 (25.7%)
Past history of suicide attempt	1,882 (12.9%)
Symptom severity:	
Mild	3,541 (24.3%)
Moderate	6,631 (45.5%)
Severe without psychotic symptoms	1,757 (12.1%)
Severe with psychotic symptoms	452 (3.1%)
Severity unspecified	2,183 (15.0%)
Parental history of psychiatric disorders:	
Unipolar depression	1,662 (11.4%)
Bipolar disorder	332 (2.3%)
Psychotic illness	339 (2.3%)
Substance abuse	1,092 (7.5%)
Anxiety disorder	945 (6.5%)

Table 3.5: *Trajectory parameters for final LCGA model*

Group	Parameter	Estimate	Standard Error	T statistic	P value
1	Intercept	6.28	0.40	15.68	<0.0001
	Linear	-10.04	0.63	-15.95	<0.0001
	Quadratic	3.25	0.27	11.90	<0.0001
	Cubic	-0.44	0.04	-9.92	<0.0001
	Quartic	0.02	0.00	8.83	<0.0001
2	Intercept	4.39	0.25	17.51	<0.0001
	Linear	-1.94	0.12	-16.68	<0.0001
	Quadratic	0.11	0.01	9.65	<0.0001
3	Intercept	3.39	0.38	8.90	<0.0001
	Linear	-5.24	0.50	-10.39	<0.0001
	Quadratic	1.66	0.18	9.26	<0.0001
	Cubic	-0.20	0.02	-7.96	<0.0001
	Quartic	0.01	0.00	6.72	<0.0001
4	Intercept	1.84	0.60	3.09	0.0020
	Linear	-0.13	0.75	-0.17	0.8627
	Quadratic	0.23	0.28	0.85	0.3982
	Cubic	-0.06	0.04	-1.62	0.1052
	Quartic	0.00	0.00	2.11	0.0351

Figure 3.11: *Patterns of 10-Year Course Trajectories of MDD*



Note. Model includes the following covariates: gender, birth year, place of birth, characteristics of first admission including age, calendar year, inpatient treatment, history of suicide attempt/self-harm, episode severity (mild, moderate, severe without psychotic features, severe with psychotic features), parental history of anxiety, depression, bipolar disorder and psychotic illness.

Table 3.6: *Frequencies of characteristics by course trajectory class membership*

Characteristic	Early Recovery (N = 10,971)	Prolonged initial illness (N =2,003)	Later recurrence (N =1,046)	Chronic Illness (N =544)
Female gender	6,754 (61.6%)	1,417 (70.7%)	716 (68.5%)	392 (72.1%)
Birth place:				
Urban	8,085 (73.7%)	1,399 (69.9%)	750 (71.7%)	376 (69.1%)
Rural	2,454 (22.4%)	536 (26.8%)	258 (24.7%)	156 (28.7%)
Other	432 (3.9%)	68 (3.4%)	38 (3.6%)	12 (2.2%)
Age at first admission, M(SD)	31.9 (9.5)	32.2 (10.0)	31.9 (9.2)	32.9 (10.0)
Inpatient treatment	2,647 (24.1%)	610 (30.5%)	235 (31.1%)	161 (29.6%)
Past history of suicide/self-harm	1,455 (13.3%)	205 (10.2%)	167 (16.0%)	55 (10.1%)
Severity of first episode:				
Mild	2,874 (26.2%)	390 (19.5%)	187 (17.9%)	90 (16.5%)
Moderate	4,872 (44.4%)	954 (47.6%)	532 (50.7%)	273 (50.2%)
Severe without psychotic features	1,194 (10.9%)	311 (15.5%)	152 (14.5%)	100 (18.4%)
Severe with psychotic features	282 (2.6%)	108 (5.4%)	34 (3.3%)	28 (5.2%)
Severity unspecified	1,749 (15.6%)	240 (12.0%)	141 (13.5%)	53 (9.7%)
Parental history of psychiatric diagnoses:				
Unipolar depression	1,198 (10.9%)	241 (12.0%)	153 (14.6%)	70 (12.9%)
Bipolar disorder	248 (2.3%)	46 (2.3%)	28 (2.7%)	10 (1.8%)
Psychotic illness	239 (2.2%)	53 (2.7%)	25 (2.4%)	22 (4.0%)
Substance abuse	847 (7.7%)	127 (6.3%)	84 (8.0%)	34 (6.3%)
Anxiety	697 (6.4%)	120 (6.0%)	92 (8.8%)	36 (6.6%)

Note: frequency estimates obtained from the unconditional LCGA model.

Table 3.7: *Predictors of course trajectory class membership*

Covariate	Prolonged initial illness vs. Early recovery OR (95% CI)	Later recurrence vs Early recovery OR (95% CI)	Chronic illness vs Early recovery OR (95% CI)	Later recurrence vs Prolonged initial illness OR (95% CI)	Chronic illness vs Prolonged initial illness OR (95% CI)	Chronic illness vs Later recurrence OR (95% CI)
Demographics:						
Female Gender	1.74 (1.55, 1.97)***	1.46 (1.24, 1.72)***	1.85 (1.49, 2.31)***	0.84 (0.69, 1.02) †	1.06 (0.83, 1.36)	1.27 (0.97, 1.67) †
Birth year	1.78 (1.64, 1.94)***	1.22 (1.01, 1.47)*	1.44 (1.37, 1.51)***	0.68 (0.64, 0.72)***	0.80 (0.74, 0.87)***	1.18 (1.09, 1.27)***
Place of birth:						
Urban	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Rural	1.32 (1.16, 1.49)***	1.12 (0.94, 1.34)	1.34 (1.08, 1.67) **	0.85 (0.70, 1.05)	1.02 (0.80, 1.30)	1.19 (0.90, 1.58)
Other	0.84 (0.62, 1.14)	0.95 (0.64, 1.41)	0.58 (0.29, 1.13)	1.13 (0.70, 1.83)	0.69 (0.33, 1.43)	0.61 (0.28, 1.32)
Characteristics of first episode:						
Age at 1st admission	1.79 (1.65, 1.94)***	1.22 (1.01, 1.46)*	1.45 (1.38, 1.53)***	0.68 (0.64, 0.72)***	0.81 (0.75, 0.88)***	1.20 (1.11, 1.29)***
Calendar year at 1st episode	0.55 (0.51, 0.60)***	0.83 (0.68, 1.00)*	0.66 (0.63, 0.69)***	1.49 (1.41, 1.58)***	1.19 (1.09, 1.30)***	0.79 (0.75, 0.84)***
Inpatient treatment at first episode	1.30 (1.15, 1.47)***	1.49 (1.26, 1.76)***	1.14 (0.91, 1.43)	1.14 (0.94, 1.39)	0.88 (0.69, 1.13)	0.77 (0.58, 1.01) †
History of suicide attempt/self-harm	0.65 (0.54, 0.79)***	1.26 (1.03, 1.54)*	0.66 (0.47, 0.93)*	1.92 (1.48, 2.50)***	1.01 (0.69, 1.49)	0.53 (0.36, 0.78)**
Severity of first episode:						
Mild	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Moderate	1.53 (1.32, 1.76)***	1.83 (1.49, 2.25)***	1.81 (1.38, 2.38)***	1.20 (0.94, 1.53)	1.19 (0.87, 1.61)	0.99 (0.70, 1.40)
Severe without psychotic symptoms	2.11(1.74, 2.55)***	2.04 (1.55, 2.68)***	2.80 (2.00, 3.93)***	0.96 (0.70, 1.33)	1.33 (0.91, 1.93)	1.38 (0.89, 2.12)
Severe wit psychotic symptoms	3.23 (2.42, 4.31)***	1.82 (1.14, 2.91)*	3.42 (2.06, 5.69)***	0.56 (0.34, 0.94)*	1.06 (0.61, 1.84)	1.87 (0.95, 3.690†
Severity unspecified	1.06 (0.88, 1.29)	1.27 (0.96, 1.68) †	0.99 (0.66, 1.47)	1.19 (0.86, 1.66)	0.93 (0.60, 1.45)	0.78 (0.48, 1.27)
Parental history of psychiatric diagnosis						
Unipolar depression	1.16 (0.97, 1.38)	1.46 (1.17, 1.81)***	1.15 (0.85, 1.56)	1.26 (0.97, 1.63) †	1.00 (0.71, 1.40)	0.79 (0.55, 1.14)
Bipolar depression	1.06 (0.72, 1.55)	1.44 (0.92, 2.26)	0.74 (0.33, 1.63)	1.36 (0.79, 2.36)	0.70 (0.29, 1.65)	0.51 (0.21, 1.28)
Psychotic illness	1.23 (0.86, 1.75)	1.01 (0.61, 1.67)	2.06 (1.22, 3.46)**	0.82 (0.46, 1.47)	1.67 (0.92, 3.04) †	2.03 (1.00, 4.12)*
Substance abuse	0.79 (0.63, 0.99)*	0.96 (0.72, 1.26)	0.89 (0.59, 1.32)	1.21 (0.86, 1.70)	1.12 (0.71, 1.75)	0.93 (0.57, 1.51)
Anxiety disorder	1.03 (0.81, 1.31)	1.43 (1.08, 1.88)*	1.00 (0.63, 1.58)	1.38 (0.99, 1.94) †	0.97 (0.58, 1.62)	0.70 (0.41, 1.19)

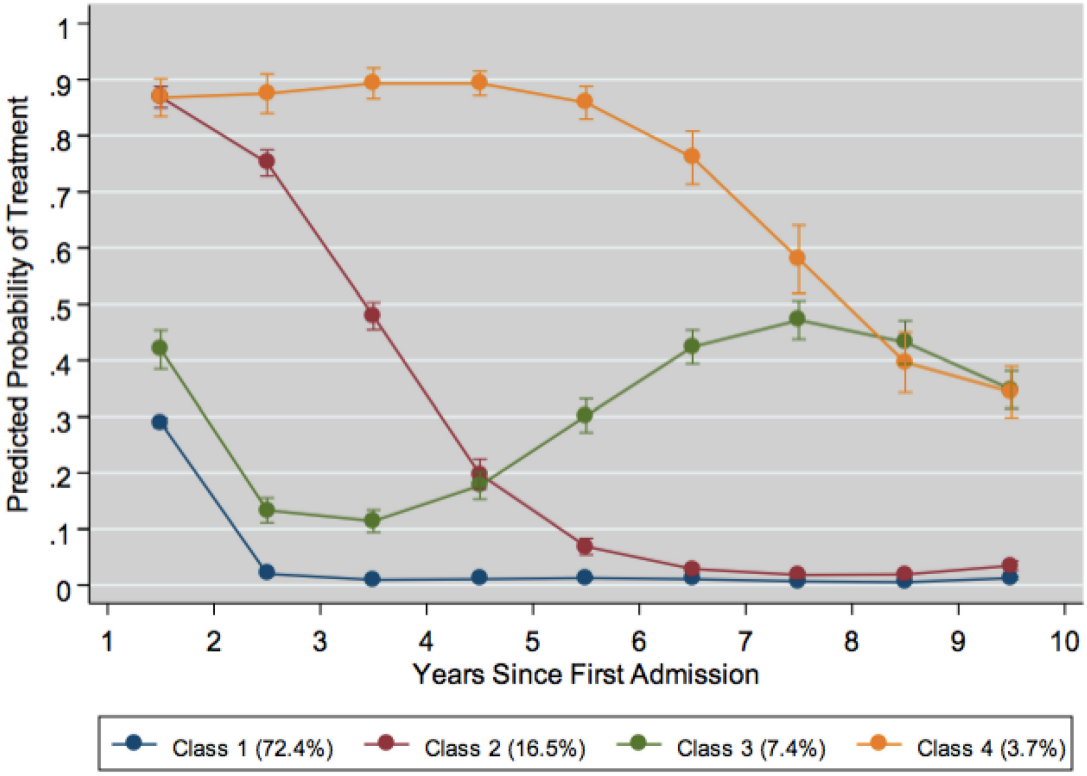
† p < .10, * p < .05, ** p < .01, *** p < .001

Sensitivity Analyses

The results of the sensitivity analyses were similar to the results in the primary study sample: Figure 3.12 shows the course trajectory patterns in a sample of MDD cases including those who otherwise met study criteria but at some point received a diagnosis of bipolar disorder or a schizophrenia spectrum disorder (note: only treatment records with an MDD diagnosis were included in the LCGA model). The trajectory patterns look almost identical to those observed in the study sample, which may be driven largely by the fact that the MDD cases without bipolar/schizophrenia diagnoses far outnumber the cases that do. It is clear that the addition of these individuals into the study sample does not meaningfully alter the trajectory patterns, which suggests these patterns are generalizable to most people who receive an MDD diagnosis.

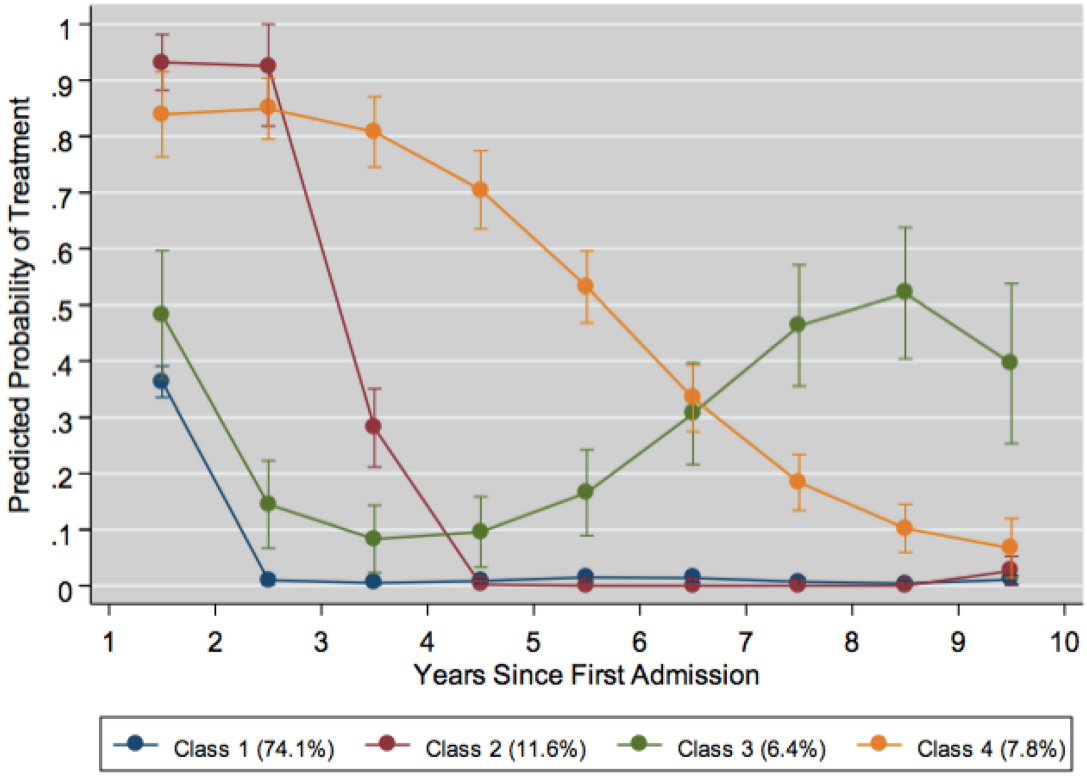
Figure 3.13 shows the course trajectory patterns in a sample of MDD cases born in 1980 or later. The trajectory patterns in this sample are similar, but not identical, to the patterns in the study sample. Trajectory patterns in classes 1 and 3 are very similar to the patterns observed in the study sample model, but class 2 is more similar to class 6 from the 6 and 7 class models (see Figures 4.7-4.8), while class 4 looks very much like class 2 from the study sample model. There does not appear to be a "chronic illness" class among individuals born in 1980 or later. These differences may indicate the presence of prevalence bias in the study sample: prevalent MDD cases may be more likely to be within the prolonged initial illness or chronic illness classes than incident cases. Research suggests that the time between MDD episodes decreases as the illness progresses (Solomon et al., 2000), possibly as a result of sensitization to external stressors (Monroe & Harkness, 2005; Post, 1992).

Figure 3.12: *Sensitivity analysis 1: Including MDD cases who also received bipolar/schizophrenia diagnoses*



Note. Bars represent 95% confidence intervals

Figure 3.13: *Sensitivity analysis 2: Individuals born in 1980 or later*



Note. Bars represent 95% confidence intervals

3.5 Discussion

In this study we examined patterns and predictors of 10-year course trajectories of MDD using latent class growth analysis. The final model contained 4 classes: *early recovery* (72.2%), *prolonged initial illness* (16.1%), *later recurrence* (8.1%) and *chronic illness* (3.6%). Female gender, rural birth place, older age at first diagnosis, inpatient treatment at first diagnosis, and severity of the initial episode were all associated with membership in the more severe trajectory classes relative to the early recovery class. Parental history of depression or anxiety predicted membership in the later recurrence class while parental history of non-affective psychosis predicted membership in the chronic illness class.

Our results suggest that over 70% of individuals who receive an MDD diagnosis in Denmark have a positive 10-year prognosis. This is more consistent with past findings from community samples, in which 10-year recurrence rates are typically lower (17.5-38%), than with previous findings from clinical samples, in which 10-year recurrence rates are high (64-67%) (Eaton et al., 2008; Hardeveld et al., 2010; Hardeveld et al., 2013; Mattisson et al., 2007; Solomon et al., 2000). One possible explanation for this is that past studies using clinical samples may have inadvertently selected patients from the most severe end of the MDD spectrum, and therefore overestimated recurrence rates among clinical cases.

A notable minority (3.6%) of cases in our sample followed a course trajectory characterized by chronic illness. This percentage may underestimate the true prevalence of chronic depression, as we relied on treatment records rather than measuring symptoms directly. Past studies that measured symptoms directly found a somewhat higher

prevalence of chronic depression: In the ECA, which followed participants actively for over 20 years, the prevalence of chronic depression was closer to 15% (Eaton et al., 2008). In the CDS, 7% of clinical cases had still not recovered from their index episode after 10 years (Mueller et al., 1999). Cronkite and colleagues (2013) followed 382 community MDD cases for 23 years and found that 27.8% followed a trajectory characterized by high symptoms.

Our results are consistent with the conclusion that although a broad range of patients with MDD at some point are treated in specialized psychiatric settings (Pedersen et al., 2014), and although the bulk of these patients have a favorable prognosis, a small but meaningful number of MDD patients experience chronic depression for years on end. This implies that a large amount of treatment for MDD goes to a minority of MDD cases, which has important implications for public health and practice. MDD is recognized as one of the most common and burdensome health conditions worldwide (Kessler et al., 2003; Murray et al., 2012; Whiteford et al., 2013); however the results of this study and those described above suggest that the public health burden of MDD may be disproportionately attributable to a small subset of cases. If this is the case, it is imperative that we develop methods for identifying these individuals as early as possible so that public health resources can be allocated in an effective manner.

Predicting a more severe course trajectory in MDD patients

Female gender was associated with a 1.5-2 fold increase in the odds of experiencing a more severe 10-year course trajectory. This is consistent with previous evidence that female gender is a risk factor both for developing depression (Weissman & Klerman, 1985) and for experiencing recurrent episodes (Kessing, Andersen, &

Mortensen, 1998; Mueller et al., 1999). Severity of the first diagnosis had a dose-response-like association with odds of membership in a more severe trajectory group. Neither gender nor severity, however, demonstrated particular usefulness in distinguishing between the three more severe course trajectories. This suggests that clinicians might view these characteristics as non-specific 'red flags' of risk for a more severe 10-year course trajectory. The fact that past history of suicide attempt/self-harm predicted membership in the later recurrence group suggests that this may be a marker for instability in future course.

Perhaps most interesting was the finding that different psychiatric disorders in parents predicted different course trajectory patterns in offspring: Specifically, parental history of depression or anxiety increased the odds of being in the later recurrence group, while parental history of non-affective psychotic disorders increased the odds of being in the chronic illness group. This raises the possibility that differences in observable MDD course trajectories are influenced by genetic factors, which is consistent with the hypothesis that depression is an etiologically heterogeneous disorder. As such, course trajectory may represent an MDD phenotype that can be used to identify more etiologically homogenous MDD populations.

Previous evidence for an association between parental psychopathology and MDD course is weak. Although Lieb et al. (2002) found an association between parental history of depression and greater severity, chronicity and recurrence of depression in offspring, only one (Maj et al., 1992) of the seven studies addressing this issue identified by Hardeveld et al. (2013) in their review of predictors of MDD recurrence found an association between family history of MDD and recurrence risk. Angst et al. (2009)

failed to find an association between parental history of depression or anxiety and MDD course patterns in the Zurich study. Rhebergen et al. (2012) found a strong effect (OR = 2.57, 95% CI [0.75, 8.76]) of family history of depression on odds of membership in the chronic severe trajectory class in the NESDA study, however the association was not statistically significant.

To the best of our knowledge, this is the first study to identify an association between parental history of non-affective psychotic disorders and chronic course trajectory in MDD. Recent evidence from the Psychiatric Genomics Consortium (Lee et al., 2013) suggests there is a genetic relationship between MDD and schizophrenia, and depression is common among schizophrenia patients (Sands & Harrow, 1999; Wassink, Flaum, Nopoulos & Andreasen, 1999). The current findings suggest that parental history of non-affective psychosis may confer risk for a subtype of MDD characterized by chronic, long-term illness. The fact remains, however, that this area of inquiry is in its infancy. Further research is needed to investigate these associations before any firm conclusions can be reached.

Methodological considerations

Several methodological considerations should be taken into account when interpreting these results: First, because we used registry data, symptoms for which individuals did not receive specialized psychiatric treatment are not accounted for in the current analyses. Second, cases who receive psychiatric treatment from their primary care doctors are not included in the PCR, therefore we may have missed milder MDD cases. Third, our decision to exclude individuals who later received schizophrenia or bipolar diagnoses may impact the generalizability of the results to all first-time MDD cases. To

evaluate this possibility, we conducted a sensitivity analysis in which we ran the LCGA models using a sample that included all MDD cases (regardless of other psychiatric diagnoses) and observed only minor differences in the results. Fourth, we were unable to incorporate information on antidepressant medications into the analyses; however, because all cases received their first MDD diagnosis between 1995 and 2002, they would all have had access to the same medications and presumably received (or were considered for receipt of) the same treatments. Further, previous research conducted using the PCR suggests that access to antidepressant medications does not influence patterns of course in affective disorders (Kessing, Hansen, & Andersen, 2004). Calendar year of first admission was included as a covariate in an attempt to control for any lingering secular trends. Finally, our results may not be generalizable to individuals with an age of onset > 60, or individuals who commit suicide, as inclusion in the study sample was contingent upon surviving for at least 10 years after the first MDD diagnosis.

Our results suggest that over 70% of individuals who receive an MDD diagnosis in Denmark have a positive 10-year prognosis. Although cause for optimism, this finding should be interpreted with caution for several reasons: first, the estimate might be inflated by the inclusion of individuals given a single depression diagnosis in error, or without careful consideration by clinicians more interested in getting their patients quickly into treatment than with the valid and reliable use of diagnostic codes. Second, it is unclear how many of the individuals in class 1 recovered fully from their depression and how many continued to receive treatment or medication in a primary care setting. Third, future research is needed to determine how many of these individuals truly

recovered and how many were responsive to antidepressant treatment and therefore able to receive care solely from their general practitioners.

Conclusions

The majority of individuals treated for MDD in inpatient and outpatient psychiatric facilities in Denmark have a low probability of being in treatment after the second year post initial diagnosis. Around 20% of MDD patients have consistently high probabilities of being in treatment, continuously or intermittently, during the first 5 years following their first diagnosis, and around 4% have a high probability of being in treatment each year for 10 years following their first diagnosis. Different parental disorders predicted different course trajectories, which suggests that observable heterogeneity in course may be indicative of underlying genetic differences in etiology.

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CHAPTER 4: Heterogeneity in 5-year course trajectories of late-onset MDD

4.1 Abstract

Objective: To examine heterogeneity in 5-year course trajectories of late-onset major depressive disorder (MDD) in a population-representative sample, and identify predictors of course trajectory class membership.

Methods: Data were obtained from the Danish civil, psychiatric and hospital population registers. The study sample included 12,200 individuals with late-onset MDD (i.e., ≥ 60 years old at first diagnosis) born in Denmark between 1898 and 1947. Mean age of first MDD diagnosis was 74.9 (*SD* = 8.9 years). Individuals ever diagnosed with bipolar disorder or schizophrenia were excluded. The primary response variable was the log odds of inpatient or outpatient MDD treatment within 6-month intervals during the 5-year period following the initial MDD diagnosis. Predictor variables included demographic characteristics, characteristics of the initial episode and past history of hospital contact for somatic illness. Trajectories were modeled using latent class growth analysis.

Results: We identified 4 distinct trajectory classes: *early recovery* (68.4%), *prolonged initial illness* (17.6%), *later recurrence* (5.7%) and *chronic illness* (8.3%). The most robust predictor of membership in any of the three more severe trajectory classes was the severity of the initial episode. Previous dementia diagnosis predicted membership in the prolonged initial illness and chronic illness classes.

Conclusion: The majority of late-onset MDD cases in Denmark have a good 5-year prognosis, however a notable subset of cases experience prolonged illness. Late-onset

MDD within the context of a pre-existing dementia diagnosis may predict course trajectories characterized by more prolonged illness.

Keywords: major depressive disorder, late-onset, latent class growth analysis, course trajectories**.**

4.2 Introduction

Depression in older adults is associated with a variety of poor health outcomes, including increased mortality (Penninx et al., 1999; Penninx et al., 2001), functional impairment (Alexopoulos, Vrontou et al., 1996), cognitive impairment (Morimoto, Kanellopoulos, Manning, & Alexopoulos, 2015) and decreased quality of life (Unutzer et al., 2000). Research on the long-term (i.e. 5+ year) trajectories of depression in older adults suggests that symptom trajectories are heterogeneous. Studies in general population samples found that the majority of older adults experience low or minimal depressive symptoms over time, others show fluctuating trajectories of increasing or decreasing symptoms, and a small but notable minority experience chronic high symptom trajectories (Andreescu, Chang, Mulsant, & Ganguli, 2008; Byers et al., 2012; Hsu, 2012; Kuchibhatla, Fillenbaum, Hybels, & Blazer, 2012; Kuo, Lin, Chen, Chuang, & Chen, 2011; Liang, Xu, Quiñones, Bennett, & Ye, 2011; Montagnier et al., 2014). Given that these studies all focused on depression trajectories in the general population, the results may not be generalizable to older adults with a clinical diagnosis of major depressive disorder (MDD).

There is reason to believe that MDD with a first onset in older adulthood (typically defined as an age of onset > 60 years) may be a distinct clinical and/or etiological entity from earlier-onset MDD. Studies from clinical (Pedersen et al., 2014) and community (Eaton et al., 1997) samples suggest that the age of onset distribution for MDD is bimodal, with one peak in early adulthood and a second, smaller peak in older adulthood. Studies also suggest that late onset depression may have a smaller genetic component (Grayson & Thomas, 2013; Musliner et al., 2015; Weissman et al., 1984).

Previous studies suggest that the long-term prognosis for clinical depression in late life is especially poor: Beekman et al. (2002) examined the 6-year natural history of depression in older adults in the Longitudinal Aging Study Amsterdam and classified 35% of the sample as "chronic" and an additional 35% as "chronic intermittent." More recently, Luppa et al. (2012) examined the 8-year natural history of depression in older adults in the Leipzig Longitudinal Study of the Aged and classified 23% as "chronic" and 17% as "intermittent." Mueller et al. (2004) examined time to recovery and recurrence in a sample of inpatient cases from the Collaborative Depression Study (CDS) and found that time to recurrence was significantly shorter for cases 65-79 at intake compared to younger individuals.

These studies examined trajectories in both prevalent and incident late life MDD cases. As such, they may have missed potential differences in course trajectories of older adults with first onset in older adulthood. Additionally, risk factors for depression or depression trajectories in older adults may be different depending on whether the episode is first onset or recurrent: Alexopoulos and colleagues (1997b), for example, have hypothesized that many late-onset MDD cases are caused by vascular pathologies which lead to white matter lesions in the brain that "predispose, precipitate or perpetuate a depressive syndrome in many elderly patients" (Alexopoulos et al., 1997a; pg. 915).

The goals of the current study were to a) characterize heterogeneity in 5-year course trajectories of late-onset (i.e. age of onset $\geq$ 60 years) MDD in a large, nationally representative sample and b) examine potential predictors of course trajectory class membership including demographic characteristics, characteristics of the initial MDD episode and previous somatic diagnoses.

4.3 Methods

Data Sources: The Danish Population Registers

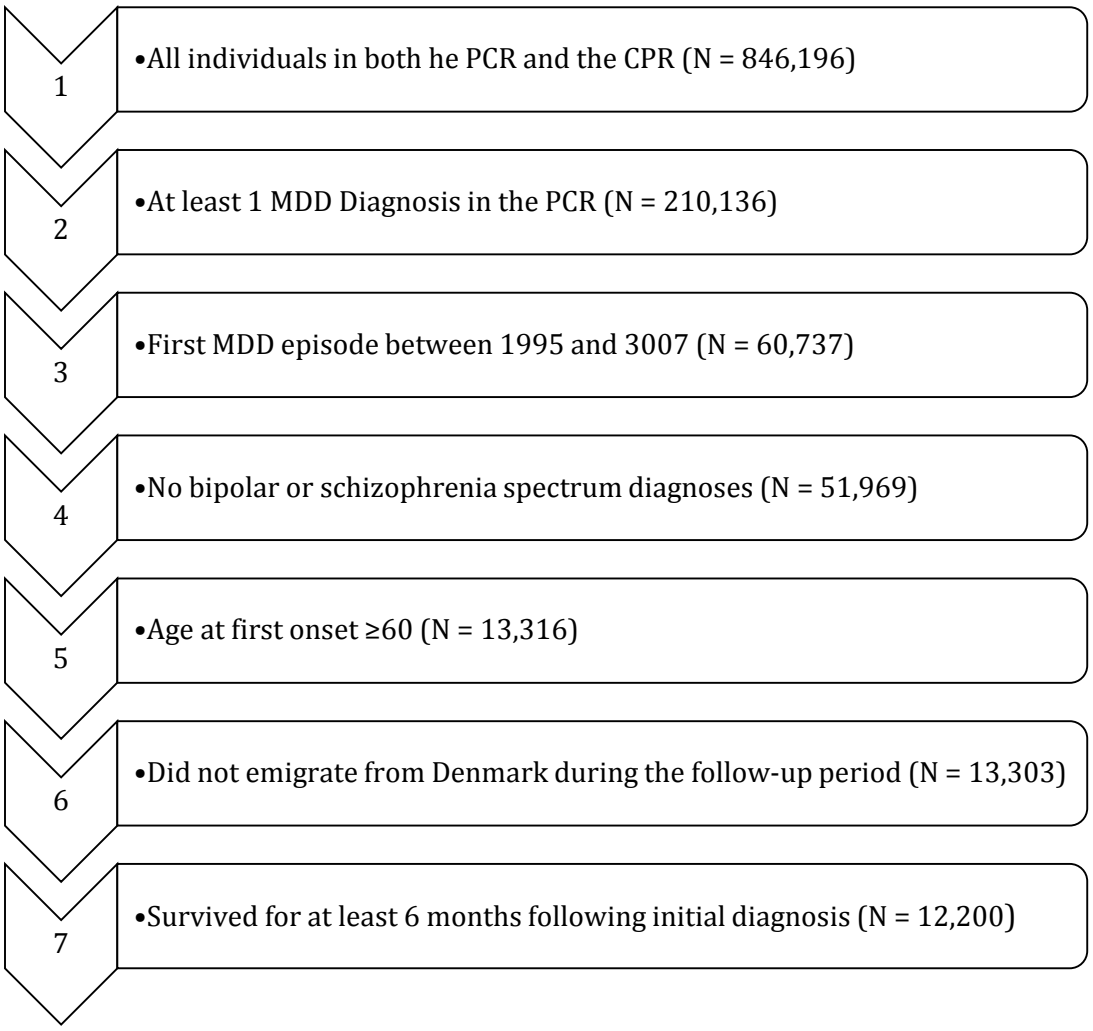
Demographic information was obtained from the Danish Civil Registry (Pedersen, 2011). MDD diagnoses and start and end dates of treatment were obtained from the Danish Psychiatric Central Research Register (Mors, Perto, & Mortensen, 2011). Information on somatic illness was obtained from the Danish National Patient Register (Lynge, Sandegaard, & Rebolj, 2011). The Danish civil and psychiatric registers have been described in greater detail elsewhere (see Chapter 3). The Danish National Patient register contains start and end dates as well as diagnoses for all inpatient hospital visits since 1977 and all outpatient contacts since 1995. Diagnoses are based on the ICD-8 from 1970 to 1993 and on the ICD-10 from 1994 to the present.

Study Sample

Individuals were included in the study sample if they met the following criteria: First, they had to have at least one main diagnosis of MDD recorded in the PCR (See Appendix A for relevant ICD-8 and ICD-10 diagnostic codes). Second, they had to have received their first MDD diagnosis between 2000 and 2007. This time frame was chosen for several reasons: first, we were interested in looking at individuals whose first MDD diagnosis occurred in older adulthood. Since 1995 was the first year during which outpatient psychiatric visits were included in the registry, we established a 5-year buffer period to help weed out prevalent MDD cases. Research suggests that the majority of MDD cases who experience a recurrence will do so within 5 years (Mattisson, Bogren, Horstmann, Munk-Jorgensen, & Nettelbladt, 2007; Mueller et al., 1999). This same buffer period was used in a study of incidence rates of psychiatric disorders in the PCR

(Pedersen et al., 2014). We chose 2007 as the cut-off year because this was the last year for which we could be certain of having 5 years of complete follow-up, including accurate vital status information, for all participants. Next, individuals could not at any point have received a bipolar or schizophrenia spectrum diagnosis (See Appendix B for exclusionary diagnostic codes) (Pedersen et al., 2014). This criterion was put in place to exclude individuals for whom the unipolar depression diagnosis was either inaccurate and later revised, or better characterized as a preliminary stage of a different psychiatric illness. Fourth, we only included individuals who were ≥ 60 years old at the time of their first MDD diagnosis in the registry. Fifth, we excluded individuals who emigrated from Denmark within the follow-up period. Finally, we restricted the sample to individuals who survived for at least 6 months following their first MDD diagnosis. Figure 4.1 illustrates the pipeline used to select the study sample. The final sample included 12,200 individuals.

Figure 4.1: *Sample Selection Pipeline*



Statistical Analysis

Course trajectories were modeled using latent class growth analyses (LCGA). Models were estimated using PROC TRAJ (Jones, Nagin, & Roeder, 2001; Jones & Nagin, 2007) in SAS 9.4 (SAS Institute Inc., Cary, NC, USA) with a binary logit distribution. PROC TRAJ uses maximum likelihood to estimate model parameters. The primary response variable was the log odds of inpatient or outpatient psychiatric treatment within each 6-month interval during the 5-year period following first diagnosis.

Model fitting and selection process

To determine the optimal number of trajectory groups, we fit models with between 1 and 7 latent classes (Figures 4.2-4.8). Each model was fit with quartic polynomial function terms for the slopes within each latent class. If a polynomial function term for a given class was not statistically significant, we ran the model without it and if the resulting model had a lower BIC, we used the later model for comparison with models containing different numbers of classes.

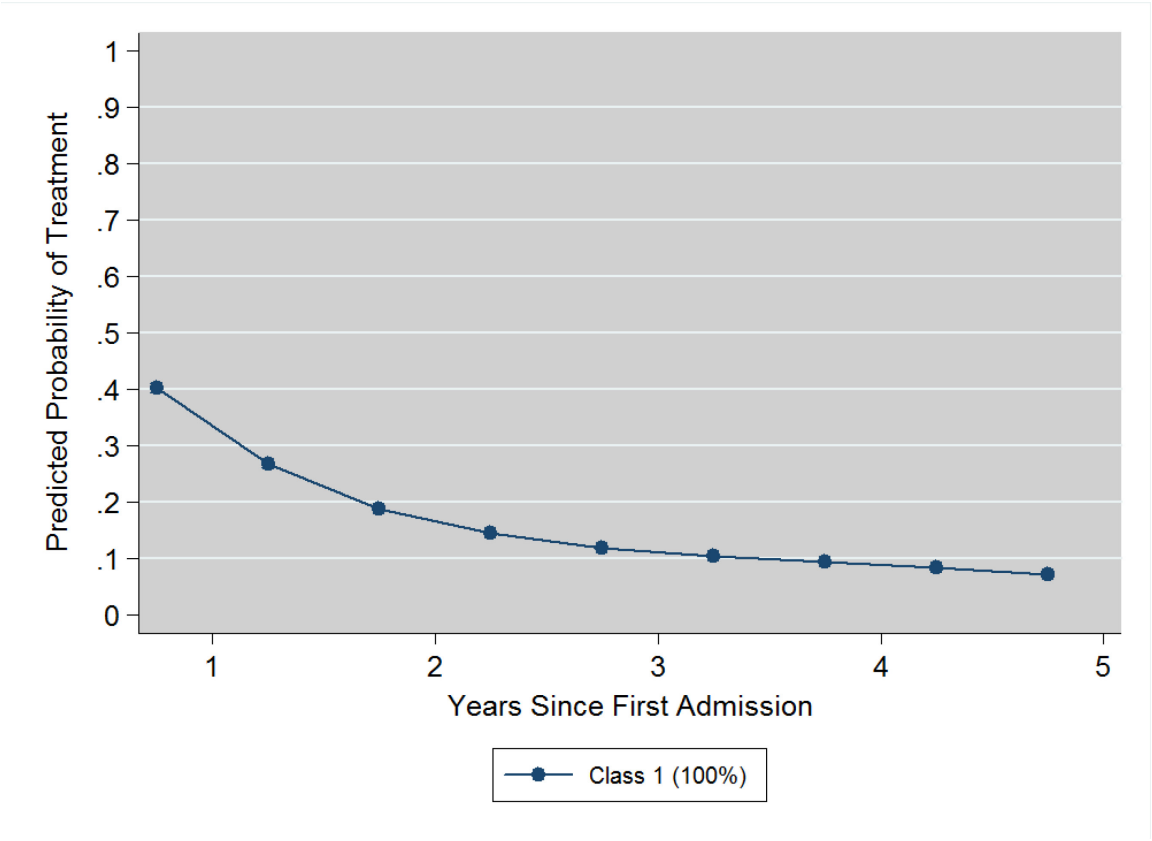
Not surprisingly given the average age of the sample, attrition due to death during the 5-year follow-up period was high (42%). To avoid bias due to non-random participant attrition (Haviland, Jones & Nagin, 2011), we incorporated a dropout model in the analyses in which the probability of death at each time point was allowed to depend on the past two time periods as well as gender, age of initial MDD diagnosis, birth place, inpatient treatment at first diagnosis and past history of heart disease, stroke, hypertension, cancer, diabetes and dementia.

When selecting the final model, we took into consideration model fit statistics with emphasis placed on the BIC (Nylund, Asparouhov, & Muthén, 2007), average

posterior probabilities of class membership (Nagin, 1999), which is a measure of the precision with which individuals are assigned to latent classes, and clinical utility. Table 4.1 shows model fit statistics for models with between 1 and 7 classes. BIC values suggested that the 5-class model was the best fit for the data, however because LCGA models do not allow for within-class variation, the BIC may overestimate the number of latent classes. Average posterior probability was highly adequate (> 80%) for all models (Table 4.2). Scree-like plots (Figures 4.9-4.10) of the AIC and BIC values (Giang & Graham, 2008; Lanza, Huang, Murphy, & Hser, 2013), point towards the 2-class model. The 3 and 4 class models showed significantly less, but still notable, improvement compared to the 2-class model, however improvement in model fit was negligible after 5 classes.

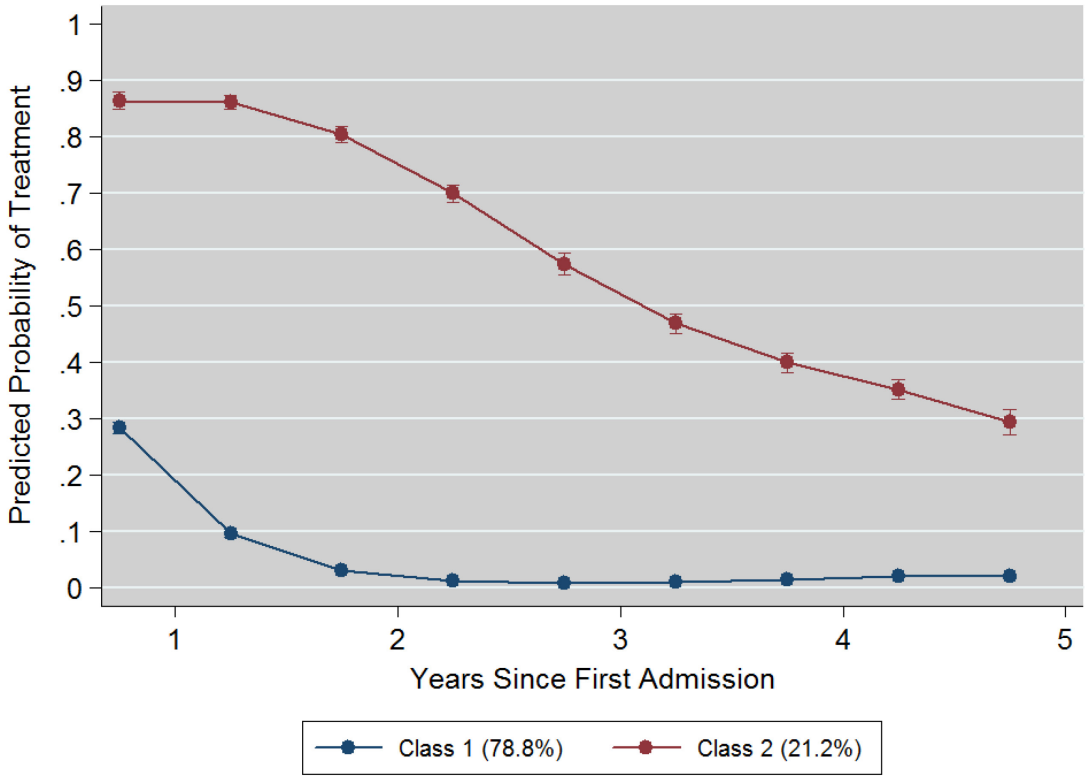
In the end, we selected the 4-class model as the final model because we felt it represented the best combination of statistical fit and clinical utility. The 4-class model demonstrated highly adequate precision (> 85% in all classes) for assigning individuals to different trajectory classes. Finally, models with more than 4 classes appeared to identify variations on existing trajectory patterns already present in the 4-class model, which led us to believe that these additional groups represented individual level, rather than group-level, variation in trajectory patterns. An examination of within-class variation (See Appendix C for a visual representation) suggested that the 4 class model captured group-level differences while allowing for individual-level variation in trajectory patterns.

Figure 4.2: *5-Year course trajectories of late-onset MDD: 1 class model*



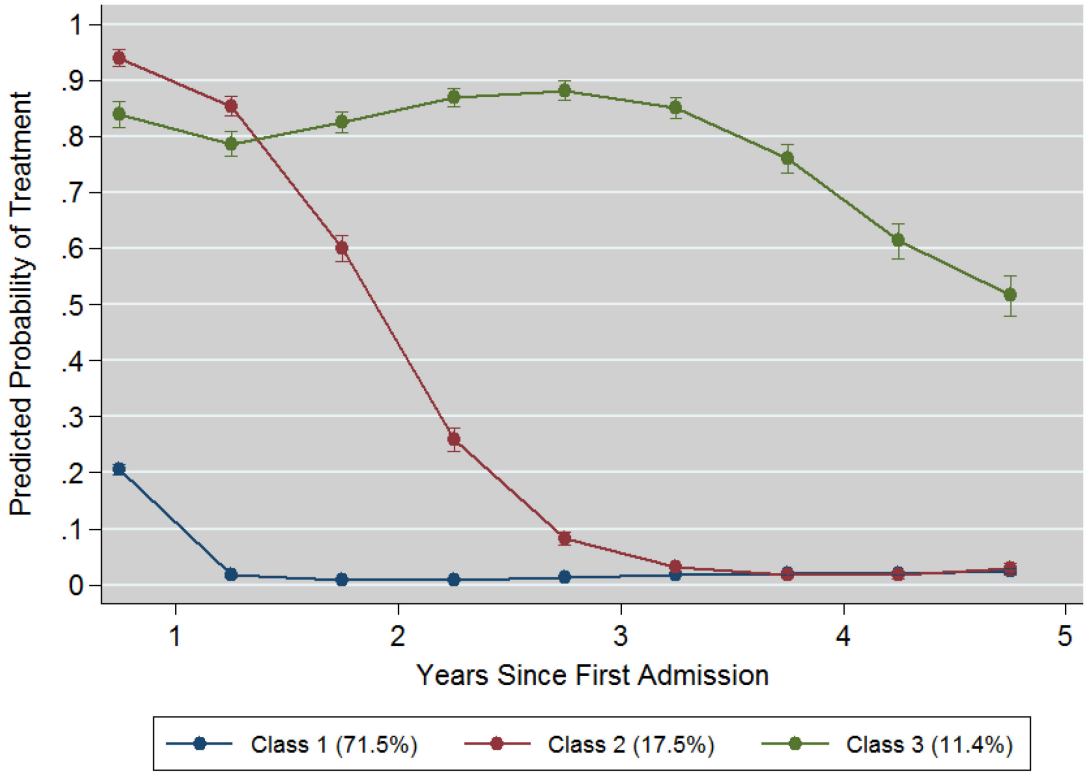
Note. Bars represent 95% confidence intervals

Figure 4.3: *5-year course trajectories of late-onset MDD: 2 class model*



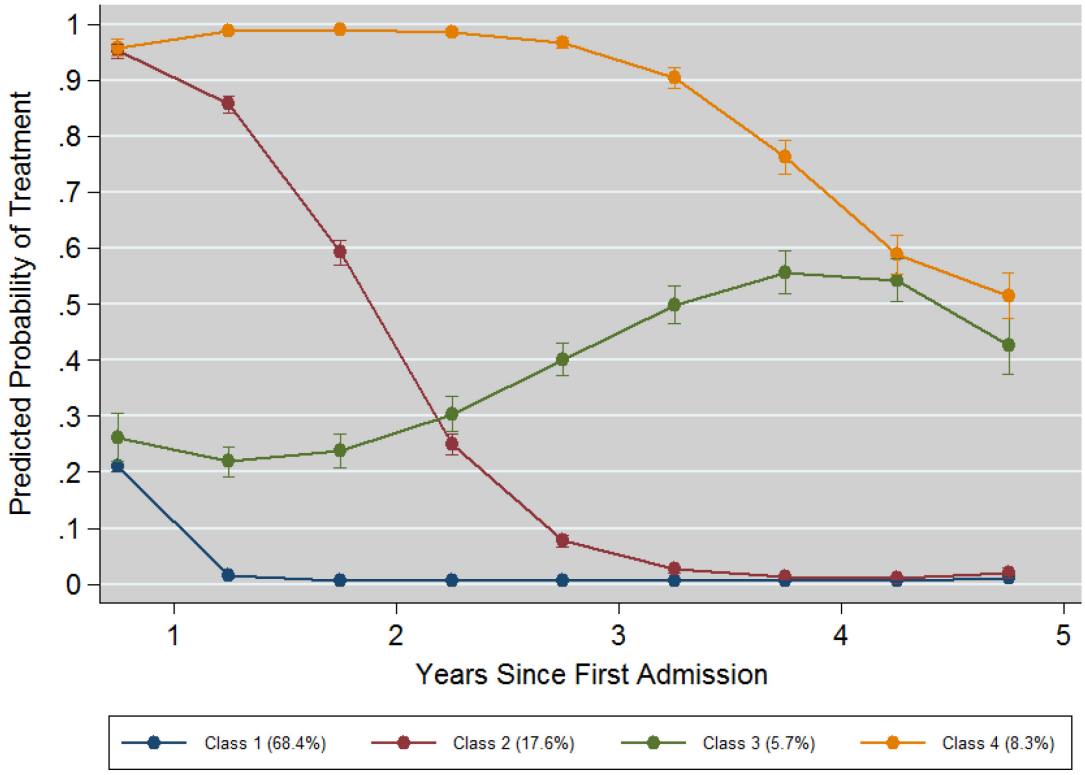
Note. Bars represent 95% confidence intervals

Figure 4.4: *5-Year course trajectories of late-onset MDD: 3 class model*



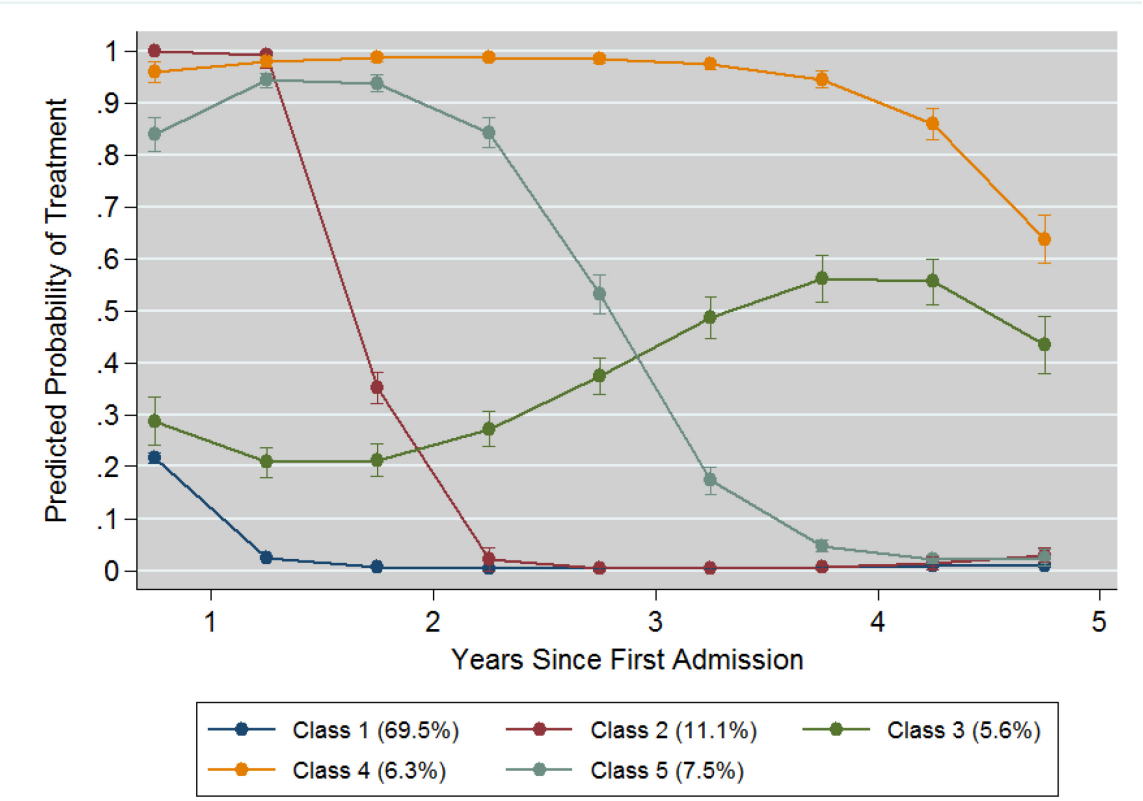
Note. Bars represent 95% confidence intervals

Figure 4.5: *5-Year course trajectories of late-onset MDD: 4 class model*



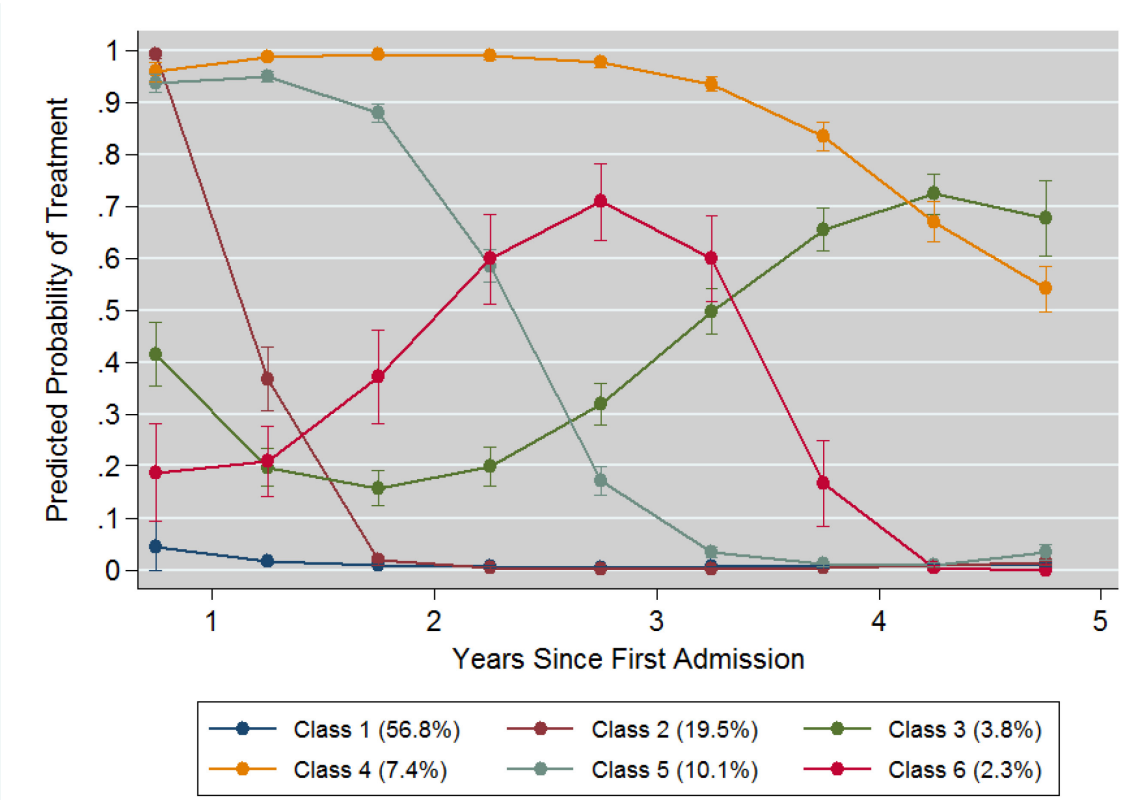
Note. Bars represent 95% confidence intervals

Figure 4.6: *5-year course trajectories of late-onset MDD: 5 class model*



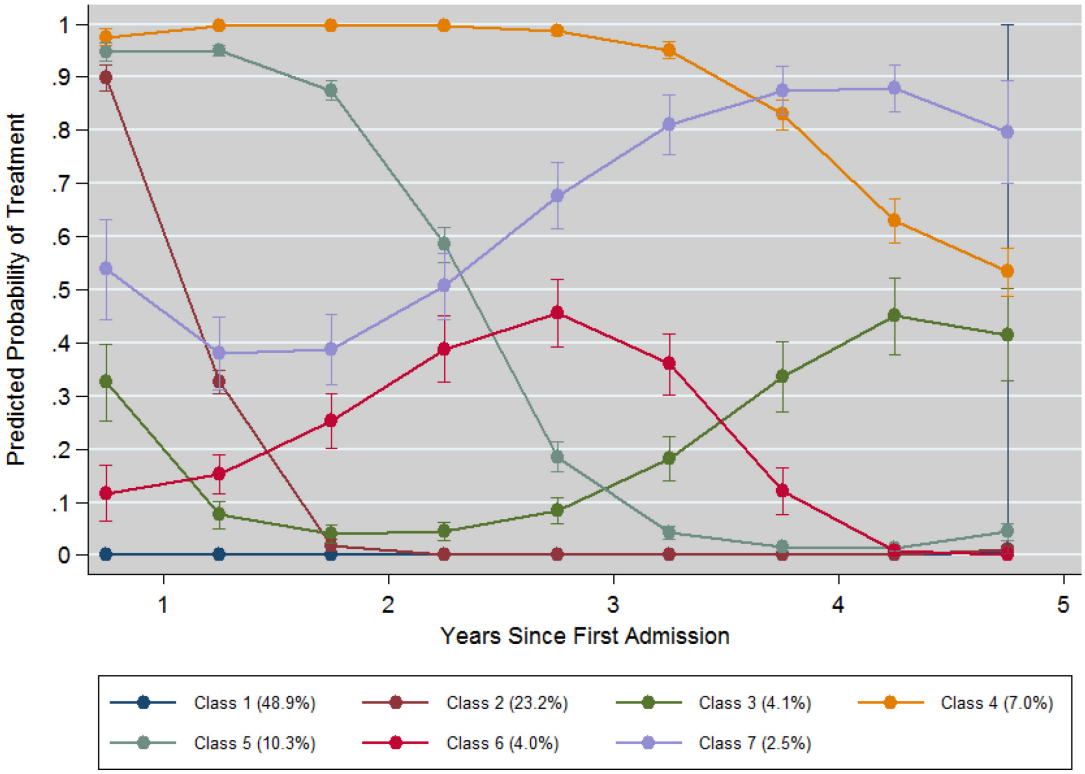
Note. Bars represent 95% confidence intervals

Figure 4.7: *5-Year Course Trajectories of early and late-onset MDD: 6 Class Model*



Note. Bars represent 95% confidence intervals

Figure 4.8: *5-Year Course Trajectories of early and late-onset MDD: 7 Class Model*



Note. Bars represent 95% confidence intervals

Table 4.1 *Comparison of fit statistics for models with between 1 and 7 classes*

# of classes	AIC	BIC	Null Model	ΔBIC	Log Bayes Factor
1	-51291.43	-51350.71	-	-	-
2	-41189.62	-41319.28	1 Class	10031.43	20062.86
3	-39093.66	-39290.00	2 Classes	2029.28	4058.56
4	-38247.59	-38499.54	3 Classes	790.46	1580.92
5	-37660.26	-37971.44	4 Classes	528.1	1056.2
6	-37673.60	-38047.77	5 Classes	-76.33	-152.66
7	-37525.65	-38080.79	6 Classes	-33.02	-66.04

Table 4.2: *Average posterior probabilities of class membership for models with 1-7 classes*

	Number of latent classes in the model													
	1		**2**		**3**		**4**		**5**		**6**		**7**	
Class	**%**	**APP**	**%**	**APP**	**%**	**APP**	**%**	**APP**	**%**	**APP**	**%**	**APP**	**%**	**APP**
1	100	1.0	78.8	0.97	71.1	0.98	68.4	0.97	69.5	0.96	56.8	0.98	48.9	0.93
2	-		21.2	0.95	17.5	0.84	17.6	0.86	11.2	0.88	19.5	0.80	23.2	0.89
3	-		-		11.4	0.88	5.7	0.90	5.6	0.89	3.8	0.90	4.1	0.85
4	-		-		-		8.3	0.89	6.3	0.86	7.4	0.83	7.0	0.85
5	-		-		-		-		7.5	0.91	10.1	0.92	10.3	0.89
6	-		-		-		-		-		2.3	0.82	4.0	0.82
7	-		-		-		-		-		-		2.5	0.86

APP = average posterior probability of group assignment within that class

Figure 4.9 *Scree-like plot of -AIC values for models with 1-7 classes*

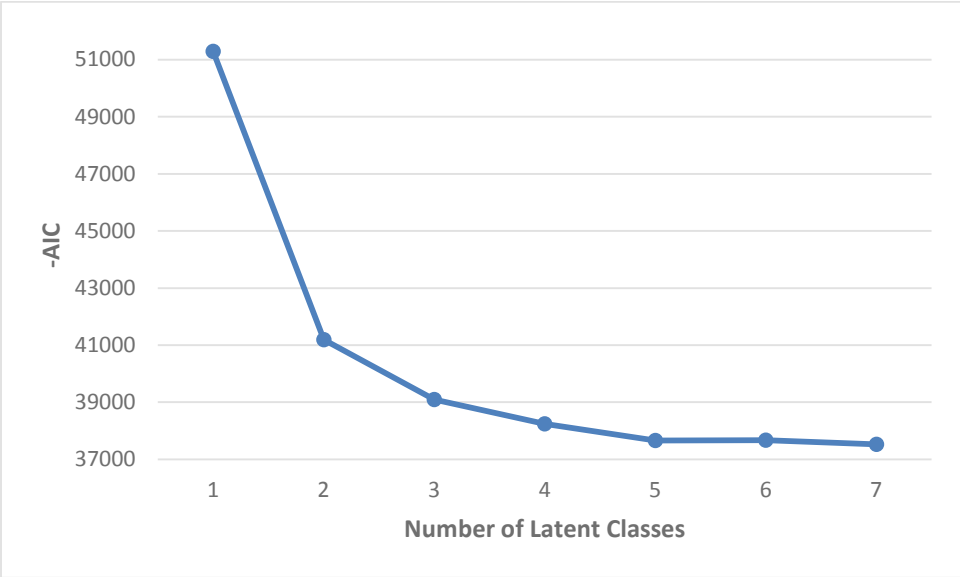
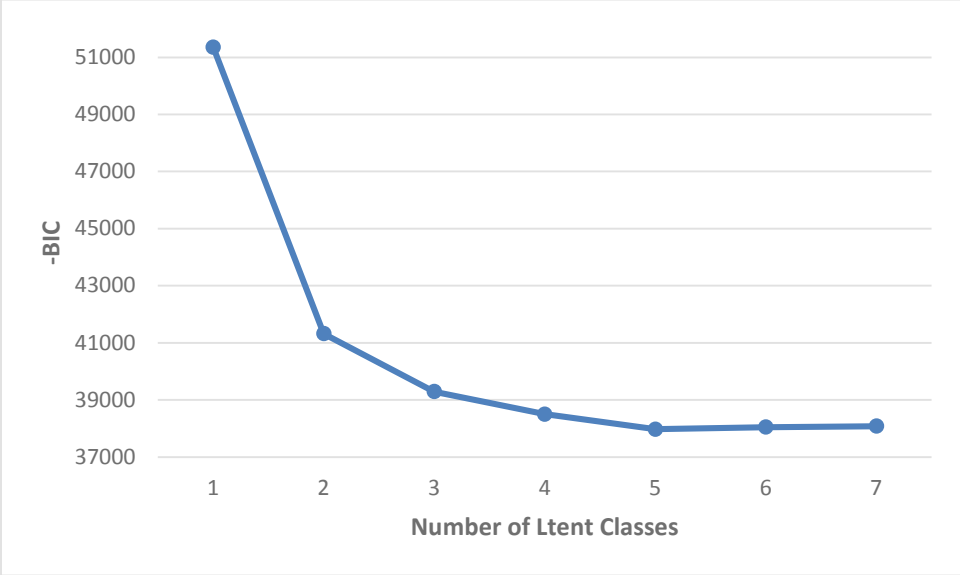


Figure 4.10: *Scree-like plot of -BIC for models with 1-7 classes*



Predictors

We examined the following variables as potential predictors of course trajectory class membership: demographic characteristics (gender (male/female), place of birth (urban, rural, other) and birth year), characteristics of the first MDD episode (calendar year of initial diagnosis, age at initial diagnosis, whether the first episode was treated in an inpatient or an outpatient setting, previous history of suicide attempt/self-harm and severity of the first episode (mild, moderate, severe without psychotic features, severe with psychotic features), and somatic diagnoses (heart disease, stroke, hypertension, cancer, diabetes mellitus, rheumatoid arthritis, or dementia). ICD-8 and ICD-10 diagnostic codes for individual somatic diseases (shown in Table 4.3) were selected after examining previous studies of somatic illness in the Danish National Patient Register (Jensen-Dahm, Gasse, Astrup, Mortensen, & Waldemar, 2014; Johannessen, Strudsholm, Foldager, & Munk-Jorgensen, 2006; Laursen, Munk-Olsen, Agerbo, Gasse, & Mortensen, 2009; Laursen & Nordentoft, 2011; Prior et al., 2014; Skaaby, Husemoen, Thuesen, Jeppesen, & Linneberg, 2015; Skaaby, Husemoen, Thuesen, & Linneberg, 2015; Thygesen, Christiansen, Christensen, Lash, & Sorensen, 2011). Only somatic diagnoses that occurred before the first MDD episode were used.

We also examined the effects of several composite measures of somatic illness, including a measure of past history of any vascular illness (heart disease, stroke, diabetes or hypertension) and the Charlson Comorbidity Index. The Charlson Comorbidity Index is a measure of chronic somatic comorbidity (Charlson, Pompei, Ales, & MacKenzie, 1987; Sundararajan et al., 2004). The index includes 19 different disease categories, each of which are assigned weights based on their severity and impact on mortality.

Scores on the Charlson Comorbidity Index are calculated by summing the weighted number of diagnoses for each individual (Table 4.4). For the purposes of this study, only diagnoses occurring before the first MDD diagnoses were used to calculate the Charlson Comorbidity Index scores. The Charlson Comorbidity index has been validated for use in the Danish registers (Thygesen et al., 2011), and has been used previously in studies of Danish register-based data (Laursen, Munk-Olsen, & Gasse, 2011).

We began by examining the frequencies of predictor variables separately for different course trajectory classes. Individuals in the study sample were assigned to course trajectory classes based on posterior probabilities. After examining differences in predictor variables descriptively, we fit a series of 4-class LCGA models incorporating the predictor variables as time-stable covariates using the "one-step" approach (Vermunt, 2010). First, we fit a model with demographic covariates only. Next we fit a model that included both demographic covariates and characteristics of the first admission. Finally we incorporated variables for past history of somatic diagnoses in three separate models: one model for individual somatic diagnoses, one model for any vascular diagnosis and one model for the Charlson Comorbidity Index scores. All three models were adjusted for demographic variables and characteristics of the first admission, with the exception of severity of the first episode, which we excluded to avoid potentially controlling for mediating effects.

Table 4.3: *ICD-8 and ICD-10 diagnostic codes used to categorize somatic diseases*

Illness category	Diagnostic Code		Condition
	ICD-8	ICD-10	
Heart Disease	391		Rheumatic fever with heart involvement
	392.0		Chorea with heart involvement
	393-398		Chronic rheumatic heart disease
	400.1		Malignant hypertension with heart involvement
	402, 404	I11.0, I13.0, I13.2	Hypertensive heart disease
	410-414	I20-I25	Ischaemic heart disease
	420-429	I27, I30-I52	Other forms of heart disease
Stroke		I60-I69	Cerebrovascular disease
	431		Intracerebral haemorrhage
	433		Cerebral Thrombosis
	434		Cerebral embolism
Hypertension	400		Malignant hypertension
	401		Essentially benign hypertension
		I10	Essential (primary) hypertension
Cancer	140-199	C00-C97	Malignant neoplasms
Diabetes	250	E10	Type 1 diabetes
	249	E11	Type 2 diabetes
Rheumatoid arthritis		M05	Seropositive rheumatoid arthritis
		M06	Other rheumatoid arthritis
	712.1		Rheumatoid arthritis with spleno-adenomegaly and leukopenia
	712.3		Other rheumatoid arthritis
	712.5		chronic rheumatoid nodular fibrositis
Dementia		F00	Dementia in Alzherimer's
		F01	Vascular dementia
		F02	Dementia in other diseases
		F03	Unspecified dementia
		F04	Organic amnestic syndrome
		F05.1	Delirium superimposed on dementia
		F06.7	Mild cognitive disorder
		G30	Alzheimer's disease
	290.0		Senile dementia
	290.1		Presenile dementia
	293.0		Cerebral arteriosclerosis

Table 4.4: *The 19 diseases included in the Charlson Comorbidity Index*

Disease Category	ICD Codes	Weight
Myocardial infarction	410, I21-I23	1
Congestive heart failure	427.09, 427.10, 427.11, 427.19, 428.99 I11.0, I13.0, I113.2, I50	1
Peripheral vascular disease	440-445, I70-I74, I77	1
Cerebrovascular disease	430-438, I60-I69, G45, G46	1
Dementia	290.09290.20, 293.09, DF0.0-DF0.4, DF0.51, G30	1
Chronic pulmonary disease	490-493, 515-518, J40-J48, J60-J67, J68.4, J70.1, J70.3, J84.1, J92.0, J96.1, J98.2, J98.3	1
Connective tissue disease	712, 716, 734, 446, 135.99, M05, M06, M08, M09, M30-M36, D86	1
Ulcer disease	530.91, 530.98, 531-535, K22.1, K25-K28.9	1
Mild liver disease	571, 573.01, 573.04, B18, K70.0, K70.4, K70.9, K71, K73, K74, K76.0	1
Diabetes mellitus	249.00, 249.06, 249.07, 249.09, 250.00, 250.06, 250.07, 250.09, E10.0, E10.1, E10.9, E11.0, E11.1, E11.9	2
Hemiplegia	344, G81, G82	2
Moderate/severe renal disease	403, 404, 580, 585, 590.09, 593.19, 753,10, 753.20, 792, I12, I13, N00, N06, N07, N11, N14, N7, N20, Q61	2
Diabetes mellitus with chronic complications	249.01, 249.06, 249.08, 250.01-250.06, E10.2, E10.9, E11.2-E11.9	2
Any tumor	140-1.94.9, C0.0-C75.9	2
Leukemia	204-207.9, C91-C95.9	2
Lymphoma	200-203.9, 275.59, C81-C85.9, C88, C90, C96	2
Moderate/severe liver disease	070.00, 070.02, 070.04, 070.06, 070.08, 573.00, 456.10, B15.0, B16.0, B16.2, B19.0, K70.4, K72, K76.6, I85	3
Metastatic solid tumor	195-199, C76, C81	3
AIDS	079.83, B21-B24.9	6

4.4 Results

Sample characteristics

Characteristics of the study sample are in Table 4.5. The sample was 67.5% female with a mean age at first MDD diagnosis of 74.9 years (*SD* = 8.9 years). Twenty eight percent received treatment for their first MDD episode in an inpatient setting, 13.0% were recorded as severe without psychotic symptoms and an additional 7.5% experienced psychotic symptoms (e.g. delusions, hallucinations, stupor) at their first admission. The most common pre-MDD somatic diagnoses, reported by 29.7% of the study sample, was heart disease followed by cancer (15.4%) and stroke (13.3%). The least common pre MDD-onset somatic illnesses were rheumatoid arthritis (1.9%), hypertension (3.7%) and dementia (5.1%).

Patterns of course trajectories

Parameters estimates from the 4-class LCGA model are shown in Table 4.6. Parameters of the dropout model are shown in Table 4.7. The largest group, containing 68.4% of the study sample, followed a course characterized by *early recovery*. These individuals had a 21% probability of inpatient or outpatient treatment within the first year following their initial diagnosis, but after that their probability of treatment dropped to less than 1%. The second largest class contained 17.6% of the sample and exhibited a course characterized by *prolonged initial illness*. Individuals in this class had over 90% probability of treatment within the first year following their initial contact. Probability of treatment in this class decreased steadily, reaching 60% by the end of year 2, and less than 10% by the end of year 3. After year 3, the probability of treatment among individuals in this class was around 1%. The third class contained 5.7% of the sample

exhibited a course characterized by *later recurrence.* These individuals had a 29% probability of being in treatment within the first year following initial contact. The probability decreased slightly, before rising to 40-50% in the final years of the follow-up period. The fourth class contained 8.3% of the sample and was characterized by *chronic illness.* Individuals in this class had over a 90% probability of treatment/admission for the first 3.5 years of follow-up. After that, probability of treatment began to decrease, but never fell below 50%.

Predictors of course trajectory class membership

Frequencies of predictor variables by course trajectory class membership are shown in Table 4.8. Odds ratios and 95% confidence intervals from LCGA models including covariates are shown in Table 4.9.

Demographic variables. Female gender was associated with membership in the later recurrence class relative to the early recovery class (OR = 1.29). Rural birthplace was associated with increased odds of membership all three of the more severe trajectory classes relative to the early recovery class (ORs: 1.24-1.39). Later birth year was associated with decreased odds of membership in the prolonged initial illness and chronic illness classes relative to the early recovery and later recurrence classes (all ORs = 0.97-0.98).

Characteristics of the first episode. Past history of suicide attempt/self-harm was associated with increased odds of membership in the early recovery group relative to the prolonged initial illness (OR = 1.47) and chronic illness (OR = 1.63) groups, and with membership in the later recurrence group relative to the chronic illness class (OR = 1.61).

Inpatient treatment at first contact was associated with increased odds of membership in the later recurrence class relative the prolonged initial illness (OR = 1.56) and early recovery (OR = 1.33) classes and with membership in the chronic illness class relative to the prolonged initial illness (OR = 1.39) and early recovery (OR = 1.19) classes. There was a dose-response-like association between severity of the first admission and course trajectory class membership, such that the more severe the initial episode, the greater the odds of membership in a more severe course trajectory relative to the early recovery class.

Past history of somatic illness. Previous dementia diagnosis was significantly associated with membership in the early recovery, prolonged initial illness and chronic illness classes relative to the later recurrence class (early recovery: 2.70; prolonged initial illness: OR = 3.22; chronic illness: OR = 2.98). None of the other individual somatic diagnoses were significantly associated with course trajectory class membership. Past history of any vascular disease and Charlson Comorbidity Index scores were not significantly associated with course trajectory class membership.

T**able 4.5:** *Characteristics of the study sample*

Characteristic	Completers (N = 7,730) N (%)	Non-completers (N = 4,470) N (%)	Total (N = 12,200) N (%)
Female gender	5,369 (69.5%)	2,865 (64.1%)	8,234 (67.5%)
Birth place:			
Urban	4,115 (53.2%)	2,195 (49.1%)	6,310 (51.7%)
Rural	3,254 (42.1%)	2,080 (46.5%)	5,334 (43.7%)
Other			
Characteristics of the first episode:			
Age at initial diagnosis (M, SD)	72.5 (8.2)	78.9 (8.6)	74.9 (8.9)
Calendar year of initial diagnosis			
2000	984 (12.7%)	643 (14.4%)	1,627 (13.3%)
2001	1,001 (13.0%)	577 (12.9%)	1,578 (12.9%)
2002	923 (11.9%)	567 (12.7%)	1,490 (12.2%)
2003	977 (12.6%)	545 (12.2%)	1,522 (12.5%)
2004	881 (11.4%)	521 (11.7%)	1,402 (11.5%)
2005	1,028 (13.3%)	537 (12.0%)	1,565 (12.8%)
2006	1,013 (13.1%)	541 (12.1%)	1,554 (12.7%)
2007	923 (11.9%)	539 (12.1%)	1,462 (12.0%)
Past history of suicide attempt/self-harm	662 (8.6%)	358 (8.05%)	1,020 (8.4%)
Inpatient treatment at first diagnosis	2,420 (31.3%)	1,024 (22.9%)	3,444 (28.2%)
Severity of first episode:			
Mild	1,352 (17.5%)	803 (18.0%)	2,155 (17.7%)
Moderate	3,400 (44.0%)	1922 (43.0%)	5,322 (43.6%)
Severe without psychotic features	1,081 (14.0%)	496 (11.1%)	1,577 (12.9%)
Severe with psychotic Features	589 (7.6%)	327 (7.3%)	916 (7.5%)
Unspecified	1,308 (16.9%)	922 (20.6%)	2,230 (18.3%)
Past history of somatic diagnoses:			
Heart disease	1,896 (24.5%)	1,721 (38.5%)	3,617 (29.7%)
Stroke	761 (9.8%)	860 (19.2%)	1,621 (13.3%)
Hypertension	230 (3.0%)	222 (5.0%)	452 (3.7%)
Cancer	992 (12.8%)	885 (19.8%)	1,877 (15.4%)
Diabetes	417 (5.4%)	415 (9.3%)	832 (6.8%)
Rheumatoid Arthritis	133 (1.7%)	101 (2.3%)	234 (1.9%)
Dementia	258 (3.3%)	359 (8.0%)	617 (5.1%)
Any vascular disease	2,640 (34.2%)	2,342 (52.4%)	4,982 (40.8%)
Charlson Comorbidity Index:			
Mean (standard deviation)	0.81 (1.25)	1.50 (1.71)	1.06 (1.48)
Median	0	0	0
Range	0-12	0-12	0-12

Table 4.6: *Parameters of the final LCGA model*

Group	Parameter	Estimate	Standard Error	T Statistic	P value
1	Intercept	4.73562	0.43616	10.858	<0.0001
	Linear	-8.17817	0.66582	-12.283	<0.0001
	Quadratic	2.40284	0.27454	8.752	<0.0001
	Cubic	-0.29942	0.04229	-7.08	<0.0001
	Quartic	0.01342	0.00217	6.193	<0.0001
2	Intercept	3.81339	0.31653	12.047	<0.0001
	Linear	-0.58613	0.2337	-2.508	0.0121
	Quadratic	-0.26509	0.05439	-4.874	<0.0001
	Cubic	0.0261	0.00377	6.914	<0.0001
3	Intercept	-0.31514	0.25284	-1.246	0.2126
	Linear	-1.0016	0.20794	-4.817	<0.0001
	Quadratic	0.30378	0.04691	6.476	<0.0001
	Cubic	-0.02137	0.00305	-7.004	<0.0001
4	Intercept	0.72304	0.41482	1.743	0.0813
	Linear	3.08205	0.36715	8.394	<0.0001
	Quadratic	-0.71333	0.07866	-9.069	<0.0001
	Cubic	0.0403	0.0048	8.389	<0.0001

Table 4.7: *Parameters of the dropout model*

Group	Parameter	Estimate	Standard Error	T Statistic	P value
1	Drop0	-8.34189	0.22033	-37.861	<0.0001
	Drop1	0.20032	0.71523	0.28	0.7794
	Drop2	-0.52295	0.17744	-2.947	0.0032
	Age	0.07074	0.00283	25.017	<0.0001
	Gender	-0.38346	0.0484	-7.922	<0.0001
	Inpatient trt	-0.14213	0.05423	-2.621	0.0088
	Heart Disease	0.21891	0.04844	4.519	<0.0001
	Stroke	0.406	0.05932	6.844	<0.0001
	Hypertension	0.14126	0.11311	1.249	0.2117
	Cancer	0.4018	0.05741	6.999	<0.0001
	Diabetes	0.43789	0.0791	5.536	<0.0001
	Dementia	0.38865	0.08927	4.354	<0.0001
2	Drop0	-9.67274	0.55522	-17.421	<0.0001
	Drop1	-0.56818	0.20125	-2.823	0.0048
	Drop2	0.10884	0.12426	0.876	0.3811
	Age	0.08878	0.00694	12.795	<0.0001
	Gender	-0.45392	0.10804	-4.201	<0.0001
	Inpatient trt	-0.27277	0.1304	-2.092	0.0365
	Heart Disease	0.32339	0.10762	3.005	0.0027
	Stroke	0.44657	0.12946	3.45	0.0006
	Hypertension	0.27367	0.20225	1.353	0.1760
	Cancer	0.11757	0.13445	0.874	0.3819
	Diabetes	0.09346	0.18908	0.494	0.6211
	Dementia	0.23425	0.18662	1.255	0.2094
3	Drop0	-7.36709	1.13443	-6.494	<0.0001
	Drop1	0.1918	0.31546	0.608	0.5432
	Drop2	0.23511	0.3273	0.718	0.4725
	Age	0.05964	0.01442	4.136	<0.0001
	Gender	-0.67603	0.23003	-2.939	0.0033
	Inpatient trt	-0.16245	0.22828	-0.712	0.4767
	Heart Disease	0.28639	0.23807	1.203	0.2290
	Stroke	0.28491	0.28261	1.008	0.3134
	Hypertension	0.1004	0.4853	0.207	0.8361
	Cancer	0.3596	0.28729	1.252	0.2107
	Diabetes	0.04256	0.46493	0.092	0.9271
	Dementia	1.10867	0.46813	2.368	0.0179
4	Drop0	-7.26857	0.7076	-10.272	<0.0001
	Drop1	-0.06709	0.24328	-0.276	0.7827
	Drop2	-0.40064	0.29568	-1.355	0.1754
	Age	0.06811	0.00849	8.023	<0.0001
	Gender	-0.45801	0.13859	-3.305	0.0010
	Inpatient trt	-0.44535	0.14361	-3.101	0.0019
	Heart Disease	0.28358	0.13941	2.034	0.0419
	Stroke	0.49315	0.16993	2.902	0.0037
	Hypertension	0.55982	0.29068	1.926	0.0541
	Cancer	0.28132	0.15904	1.769	0.0769
	Diabetes	0.3466	0.24849	1.395	0.1631
	Dementia	0.07523	0.27828	0.27	0.7869

Table 4.8: *Frequencies of characteristics by course trajectory class membership*

Characteristic	Early Recovery (N = 8,454)	Prolonged initial illness (N =2,200)	Later recurrence (N =540)	Chronic Illness (N =1,006)
Female gender	5,612 (66.4%)	1,534 (69.7%)	391 (72.4%)	697 (69.3%)
Birth place:				
Urban	4,543 (53.7%)	1,065 (48.4%)	259 (48.0%)	443 (44.0%)
Rural	3,517 (41.6%)	1,052 (47.8%)	254 (47.05)	511 (50.8%)
Other	394 (4.7%)	83 (3.8%)	27 (5.0%)	52 (5.2%)
Age at first admission, M(SD)	74.4 (8.9)	76.6 (8.9)	73.3 (8.4)	76.0 (8.1)
Inpatient treatment	2,343 (27.7%)	586 (26.65)	195 (36.1%)	320 (31.8%)
Past history of suicide/self-harm	775 (9.2%)	140 (6.4%)	48 (8.9%)	57 (5.7%)
Severity of first episode:				
Mild	1,587 (18.8%)	338 (15.4%)	84 (15.6%)	146 (15.4%)
Moderate	3,662 (43.3%)	997 (45.3%)	228 (42.25)	435 (43.2%)
Severe without psychotic features	993 (11.8%)	324 (14.7%)	95 (17.6%)	165 (16.4%)
Severe with psychotic features	536 (6.3%)	203 (9.2%)	54 (10.0%)	123 (12.2%)
Severity unspecified	1,676 (19.8%)	338 (15.4%)	79 (14.6%)	137 (13.6%)
Somatic diagnoses:				
Heart disease	2,513 (29.7%)	663 (30.1%)	142 (26.3%)	299 (29.7%)
Stroke	1,128 (13.3%)	295 (13.4%)	63 (11.7%)	135 (13.4%)
Hypertension	291 (3.4%)	93 (4.2%)	23 (4.3%)	45 (4.5%)
Cancer	1,297 (15.3%)	342 (15.6%)	71 (13.2%)	167 (16.6%)
Diabetes	591 (7.0%	147 (6.7%)	28 (5.2%)	66 (6.6%)
Rheumatoid arthritis	161 (1.9%)	47 (2.1%)	12 (2.2%)	14 (1.4%)
Dementia	411 (4.95)	136 (6.2%)	14 (2.6%)	56 (5.6%)
Vascular disease	3,472 (41.1%)	916 (41.6%)	193 (35.7%)	401 (39.9%)
Charlson Comorbidity Index (M, SD)	1.07 (1.47)	1.09 (1.49)	0.84 (1.29)	1.10 (1.55)

Note: frequencies obtained from the unconditional model

Table 4.9: *Predictors of course trajectory class membership*

Covariate	Prolonged initial illness vs. Early recovery OR (95% CI)	Later recurrence vs Early recovery OR (95% CI)	Chronic illness vs Early recovery OR (95% CI)	Later recurrence vs Prolonged initial illness OR (95% CI)	Chronic illness vs prolonged initial illness OR (95% CI)	Chronic illness vs. Later recurrence OR (95% CI)
Female gender	1.11 (0.99, 1.25)†	1.29 (1.03, 1.62)*	1.10 (0.94, 1.29)	1.16 (0.91, 1.48)	0.99 (0.81, 1.20)	0.85 (0.65, 1.11)
Place of birth						
Urban	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Rural	1.28 (1.15, 1.43)***	1.24 (1.02, 1.51)*	1.39 (1.20, 1.61)***	0.97 (0.78, 1.20)	1.09 (0.91, 1.30)	1.12 (0.89, 1.43)
Other	0.93 (0.71, 1.23)	1.26 (0.82, 1.94)	1.36 (0.98, 1.87)	1.35 (0.83, 2.21)	1.45 (0.96, 2.20) †	1.07 (0.64, 1.80)
Birth year	0.98 (0.97, 0.99)***	1.01 (1.00, 1.02)†	0.98 (0.97, 0.98)***	1.03 (1.02, 1.04)***	1.00 (0.99, 1.01)	0.97 (0.95, 0.98)***
Calendar year of initial diagnosis	1.03 (0.90, 1.17)	0.95 (0.81, 1.12)	1.00 (0.81, 1.25)	0.93 (0.81, 1.06)	0.98 (0.74, 1.30)	1.06 (0.94, 1.19)
Age at initial diagnosis	1.03 (0.91, 1.18)	0.99 (0.84, 1.17)	1.00 (0.81, 1.23)	0.96 (0.84, 1.10)	0.97 (0.73, 1.27)	1.00 (0.91, 1.11)
Past history of suicide attempt/self-harm	0.68 (0.54, 0.84)***	0.93 (0.67, 1.30)	0.58 (0.43, 0.79)***	1.38 (0.94, 2.02)†	0.86 (0.60, 1.24)	0.62 (0.40, 0.96)*
Inpatient treatment at first diagnosis	0.85 (0.75, 0.97)***	1.33 (1.07, 1.66)*	1.19 (1.00, 1.40)*	1.56 (1.22, 2.00)***	1.39 (1.13, 1.71)**	0.89 (0.68, 1.16)
Severity of initial episode						
Mild	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Moderate	1.35 (1.16, 1.58)***	1.14 (0.86, 1.50)	1.38 (1.11, 1.73)**	0.84 (0.62, 1.15)	1.02 (0.78, 1.34)	1.22 (0.86, 1.73)
Severe without psychotic features	1.73 (1.42, 2.11)***	1.68 (1.20, 2.35)**	2.24 (1.72, 2.92)***	0.97 (0.67, 1.41)	1.30 (0.94, 1.78)	1.33 (0.88, 2.02)
Severe with psychotic Features	2.00 (1.58, 2.53)***	1.82 (1.22, 2.71)**	2.74 (2.04, 3.68)***	0.91 (0.59, 1.41)	1.37 (0.96, 1.96) †	1.50 (0.94, 2.41)†
Severity unspecified	0.88 (0.73, 1.06)	0.90 (0.63, 1.28)	0.97 (0.74, 1.28)	1.02 (0.69, 1.51)	1.11 (0.79, 1.54)	1.08 (0.70, 1.67)
Somatic diagnosis[b]:						
Heart disease	0.92 (0.81, 1.04)	0.97 (0.76, 1.23)	0.94 (0.79, 1.11)	1.06 (0.81, 1.37)	1.02 (0.82, 1.27)	0.97 (0.73, 1.29)
Stroke	1.00 (0.85, 1.17)	1.02 (0.74, 1.41)	0.93 (0.73, 1.18)	1.03 (0.72, 1.45)	0.93 (0.69, 1.26)	0.91 (0.62, 1.34)
Hypertension	1.38 (1.05, 1.81)*	1.46 (0.86, 2.47)	1.05 (0.68, 1.64)	1.06 (0.60, 1.86)	0.77 (0.45, 1.29)	0.72 (0.37, 1.40)
Cancer	0.95 (0.82, 1.11)	0.90 (0.66, 1.24)	1.10 (0.90, 1.35)	0.95 (0.68, 1.33)	1.15 (0.90, 1.48)	1.22 (0.85, 1.75)
Diabetes	0.96 (0.77, 1.20)	0.77 (0.48, 1.23)	0.90 (0.64, 1.26)	0.80 (0.48, 1.33)	0.94 (0.62, 1.43)	1.17 (0.67, 2.07)
Rheumatoid Arthritis	1.11 (0.76, 1.63)	1.39 (0.74, 2.61)	0.69 (0.35, 1.34)	1.24 (0.62, 2.51)	0.62 (0.29, 1.32)	0.50 (0.20, 1.21)
Dementia	1.21 (0.95, 1.53)	0.37 (0.16, 0.88)*	1.11 (0.77, 1.58)	0.31 (0.13, 0.75)**	0.92 (0.59, 1.43)	2.98 (1.19, 7.45)*
Any vascular disease	0.95 (0.85, 1.06)	0.93 (0.75, 1.14)	0.87 (0.74, 1.02)†	0.98 (0.78, 1.23)	0.92 (0.76, 1.12)	0.94 (0.73, 1.21)
Charlston Comorbidity Index	0.99 (0.95, 1.03)	0.93 (0.86, 1.01)†	1.00 (0.94, 1.06)	0.94 (0.86, 1.03)	1.01 (0.94, 1.09)	1.07 (0.98, 1.18)

[a]Model adjusted for gender, birth year, and birth place (urban, rural, other)

[b]Models adjusted for gender, birth year, place of birth (urban, rural, other), calendar year of first admission, past history of suicide/self-harm, and inpatient treatment.

†p < .10, *p < .05, **p < .01, ***p < .001

4.5 Discussion

The goal of this study was to examine patterns and predictors of 5-year course trajectories of late-onset MDD. Results supported a model with four classes: *early recovery (68.4%), prolonged initial illness (17.6%), later recurrence (5.7%)* and *chronic illness (8.3%).* These results suggest that the majority of individuals with late onset MDD have a positive prognosis, with little to no probability of requiring treatment after the first year following their initial diagnoses. A small but notable proportion of cases, however, may require treatment almost continuously throughout the 5-year period following their initial diagnosis. This means that a large proportion of specialized treatment for late-onset MDD in Denmark goes to a small proportion of cases.

The results of this study stand in contrast to previous studies of the long-term course in late-life MDD, which reported a very poor prognosis for older adults (Beekman et al., 2002; Luppa et al., 2012; Mueller et al., 2004). Many of the cases evaluated in these previous studies were likely prevalent rather than incident, and may have had multiple previous episodes of MDD before the start of the study. Research suggests that the time to recurrence decreases with each additional MDD episode (Solomon et al., 2000), which could explain why older individuals would appear to have a more chronic course. This is consistent with the Kindling Hypothesis (Monroe & Harkness, 2005; Post, 1992), which suggests that episodes of depression sensitize the brain in such a way as to make subsequent episodes more likely.

Predictors of course trajectories of late-onset MDD

The most robust predictor of course trajectory class membership was the severity of the initial episode. Gender, age at initial diagnosis and calendar year at initial

diagnosis were not strongly associated with course trajectory class membership. This is somewhat surprising, considering that these variables were significantly associated with 10-year course trajectory class membership among individuals with earlier onset MDD (Chapter 3).

Unlike previous studies of trajectories of depressive symptoms in older adults (Byers et al., 2012; Hsu, 2012; Liang et al., 2011; Montagnier et al., 2014), we found little evidence for an association between course trajectory class membership and either individual somatic diagnoses or the overall burden of somatic comorbidity. It is possible that individuals with comorbid somatic diseases are less likely to receive specialized psychiatric care for depression because they receive medication management from the same doctor who treats them for other medical conditions.

MDD course trajectories and dementia

Of the seven pre-existing diagnoses examined as potential predictors of late-onset MDD course trajectory, only dementia emerged as a strong, consistent predictor of course trajectory class membership: individuals with a previous dementia diagnosis were around 3 times as likely to be in the prolonged initial illness and chronic illness classes relative to the later recurrence class. They were also more likely to be in the early recovery class relative to the later recurrence class, which may indicate that some dementia cases either recover or receive MDD treatment from other healthcare providers.

The association between depression and dementia is well established: Depression is highly prevalent among individuals with Alzheimer's disease (Starkstein, Jorge, Mizrahi, & Robinson, 2005; Zubenko et al., 2003) and mild cognitive impairment (Gabryelewicz et al., 2004). In addition, depression, particularly late-onset depression,

has been shown to predict the subsequent onset of dementia and Alzheimer's disease (Leinonen et al., 2004; Ownby, Crocco, Acevedo, John, & Loewenstein, 2006; Tam & Lam, 2013; Zalsman et al., 2000), although whether depression represents a risk factor for dementia, a prodromal phase of dementia or Alzheimer's disease (Heser et al., 2013; Potter et al., 2013) or whether both disorders are caused by a third factor such as white matter lesions (Gudmundsson et al., 2015), inflammation (Dobos, Korf, Luiten, & Eisel, 2010) or plasma Amyloid beta-42 (Blasko et al., 2010) remains unclear.

Several previous studies found evidence that MDD in dementia patients is more likely to be characterized by a chronic course, at least in the short term (Ames, Ashby, Mann, & Graham, 1988; Ballard, Patel, Solis, Lowe, & Wilcock, 1996; Starkstein et al., 1997). This conclusion is not universally supported, however. Janzing and colleagues (2000) specifically compared the 1-year course of depression between patients with and without dementia, and found no differences between the two. In a similar vein, Alexopoulos et al. (1996) found that cognitive impairment did not predict time to recovery in older MDD cases, although they specifically excluded patients with severe dementia. In terms of long-term trajectories, Beekman et al. (2002) found that cognitive impairment at baseline was associated with a chronic course type over their 6-year follow-up of community MDD cases, which is consistent with the findings of the current study.

Another possible explanation for the finding that MDD cases with a previous dementia diagnosis were more likely to be in the chronic illness or prolonged initial illness classes is that some of these individuals may have been misdiagnosed: Research suggests that MDD with psychotic features can in some cases be mistaken for dementia

(Wagner, McClintock, Rosenquist, McCall, & Kahn, 2011), and psychotic features were associated with increased odds of membership in the chronic illness and prolonged initial illness classes. This explanation is seemingly contradicted, however, by the finding that the odds of membership in the later recurrence group relative to the early recovery group were significantly higher for individuals with psychotic features but among individuals with a previous dementia diagnosis.

Limitations

There are several important limitations that should be taken into account when interpreting the results of this study. First, as with all register-based studies, we did not measure MDD directly, but rather used specialized psychiatric treatment as an indicator of illness. As a result, individuals who either a) received treatment for depression from their primary care doctors or b) did not receive any treatment for their depressive symptoms were not included in the study sample. We therefore likely missed an unknown number of cases from the milder end of the depression spectrum. However there is reason to believe that the sample is representative of most moderate and severe cases: First, treatment in Denmark is free, meaning there are few, if any, financial barriers to receiving specialized psychiatric care. Second, Denmark has a comprehensive and highly developed healthcare system and treatment is readily available in all areas, even rural ones. Third, although stigma towards mental illness may deter some individuals from seeking care, the Danish population is extremely culturally homogenous, which means that unlike the racially, politically, religiously and culturally diverse United States, there are unlikely to be systematic differences within the Danish population in terms of who does or does not seek treatment.

Second, although we took measures to ensure we were selecting a sample of truly first-onset cases, some individuals may have experienced episodes of MDD before the advent of the registry. We can say for certain only that the individuals in the sample did not receive inpatient MDD treatment between 1970 and 2000, or outpatient treatment between 1995 and 2000. Previous research suggests that the majority of individuals who experience a recurrent MDD episode do so within 5 years (Mattisson et al., 2007; Mueller et al., 1999). In addition, time to recurrence decreases with each episode (Solomon et al., 2000), therefore individuals in the sample, who were well past the average age of onset for MDD in 1995, would be even more likely than a random sample of MDD cases to recur within the 5-year buffer window.

Conclusions

The results of this study suggest that the majority (68%) of late-onset MDD cases have a positive prognosis, however a substantial minority experience course trajectories characterized by prolonged initial periods of illness (17.6%), later recurrence (5.7%) and chronic illness (8.3%). The most robust predictor of membership in any of the three more severe trajectory classes was the severity of the initial episode. Individuals with a pre-existing dementia diagnosis were more likely to have a trajectory characterized by prolonged illness periods.

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CHAPTER 5: Discussion

5.1 Summary of findings

The goals of this dissertation project were to a) review evidence from previous studies that used group-based trajectory modeling to characterize heterogeneity in long-term trajectories of depression, and b) apply a group-based trajectory modeling technique to examine patterns and predictors of long-term trajectories of course in MDD cases in the Danish Psychiatric Register.

A critical review of the literature identified 20 studies that examined heterogeneity in trajectories of depressive symptoms with follow-up periods of 5 or more years, and sample sizes of 200 or greater. Seven of the studies focused on heterogeneity in trajectories of depressive symptoms in adolescents, 3 looked exclusively at mothers, 3 looked at adults and 7 looked at older adults. Most of the studies identified either 4 or 6 distinct trajectory patterns: a class with consistently low or minimal depressive symptoms, usually containing the majority of the sample, a class with persistently high symptoms, typically containing <10% of the sample, and additional smaller classes with unstable trajectories (increasing or decreasing symptoms). Female gender, low SES, younger age, non-white race and stressful life events predicted membership in trajectory classes with higher symptoms. Among older adults, chronic diseases at baseline also predicted membership in course trajectory classes with higher symptoms.

All of the studies identified in this review examined heterogeneity in trajectories of depressive symptoms in general population samples. As a result, they may not be generalizable to individuals with clinical depression, or necessarily pertain to questions

regarding illness course (i.e. the ebb and flow of psychopathology (Eaton, 2002)) between first onset and outcome).

In papers 2 and 3, we extended the results of the studies reviewed in paper 1 by using latent class growth anlysis (LCGA) to examining patterns and predictors of long-term course trajectories among individuals diagnosed with major depressive disorder (MDD) in the Danish Psychiatric Registry. In paper 2 we characterized heterogeneity in 10-year trajectories of inpatient and outpatient treatment in MDD cases with onset before age 60. We identified 4 trajectory patterns: early recovery (73.1%), prolonged initial illness (15.2%), later recurrence (8.1%) and chronic illness (3.6%). Predictors of a poor course trajectory (relative to the early recovery class) included female gender, later birth year, older age at initial diagnosis, increased severity of initial episode and inpatient treatment at first diagnosis. Past history of suicide/self-harm and later calendar year at initial diagnosis predicted membership in the early recovery and later recurrence groups. Parental history of depression and anxiety predicted membership in the later recurrence group, and parental history of psychotic illness predicted membership in the chronic illness group.

In paper 3 we characterized heterogeneity in 5-year trajectories of inpatient and outpatient treatment in late-onset MDD cases (≥ 60). Again, we identified 4 trajectory patterns: early recovery (68.4%), prolonged initial illness (17.6%), later recurrence (5.7%) and chronic illness (8.3%). Severity of the initial episode predicted membership in all three poor course trajectory classes relative to the early recovery class. Female gender was associated with membership in the later recurrence class only. Rural birth

place, earlier birth year, and past history of a dementia diagnosis predicted membership in the prolonged initial illness and chronic illness groups.

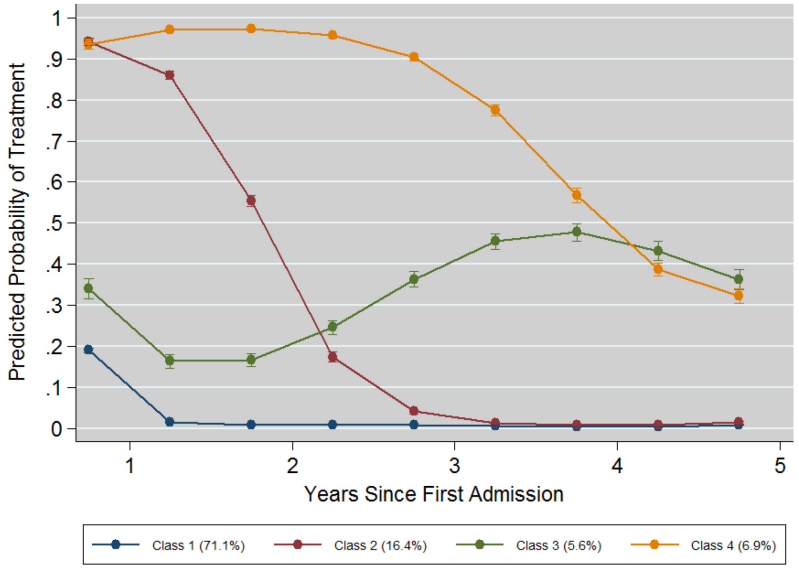
5.2 Discussion of findings

Comparison of trajectories of early onset vs. late onset MDD

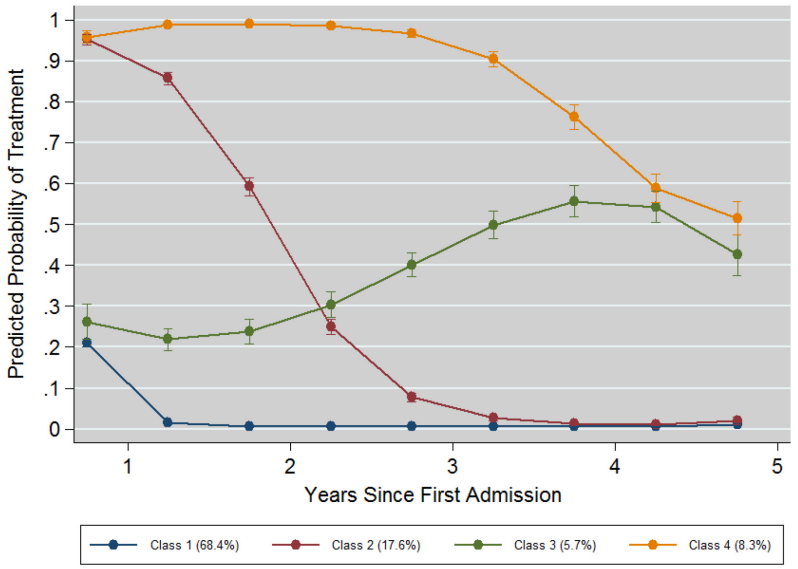
Trajectory patterns for earlier and late onset MDD were very similar to one another. To facilitate comparison and help clarify whether differences between the two were due to the variations in length of follow-up (10 years vs. 5 years) or the intervals within which the probabilities of inpatient or outpatient treatment were calculated (1 year vs. 6 months), we used the selection criteria from paper 3 to identify a sample of individuals with early onset MDD, and modeled 5-year trajectories at 6-month intervals within this sample. Figure 5.1 shows 5-year trajectories for early onset and late onset MDD cases. As anticipated, they are highly similar to one another, reaffirming that course trajectory patterns, as measured by inpatient and outpatient treatment, do not vary significantly by age of MDD onset. There were some minor differences - the probability of treatment in the two classes characterized by prolonged illness periods (classes 2 and 4) began to decrease later among the late-onset cases, and the fluctuation in the later recurrence group was more pronounced among the earlier-onset cases. It is difficult to determine whether or not these differences are clinically meaningful. A larger proportion of late-onset cases were in the chronic illness class, which is consistent with the finding in paper 2 that higher age of onset was associated with increased odds of membership in the chronic illness and prolonged initial illness groups.

Figure 5.1: *Comparison of 5-year course trajectories in early onset and late onset MDD cases*

a) 5-year course trajectories in early onset cases (N = 36,027)



b) 5-year course trajectories in late-onset cases (N = 12,220)



Overall, demographic variables had a stronger impact on the odds of course trajectory class membership in earlier onset cases than in late-onset cases. Birth year had the opposite effect on course trajectory class membership in early vs. late onset cases: among individuals with an age of onset < 60, later birth year was significantly associated with increased odds of membership in a poor trajectory class, particularly the prolonged initial illness or chronic illness classes. In late-onset MDD cases, later birth year was protective against membership in the prolonged initial illness and chronic illness classes. This despite the fact that the time frames of analysis (1995-2002 in paper 2, 2000-2007 in paper 3) overlapped. Higher age and earlier calendar year at first diagnosis were both associated with increased odds of membership in a more severe course trajectory class among earlier onset cases, but among late-onset cases there was no effect of either variable on course trajectory class membership. Severity of the initial episode and past history of suicide attempt/self-harm showed a similar pattern in both late and earlier onset cases, with higher severity associated with increased odds of membership in a more severe trajectory class, and past history of suicide attempt/self-harm associated with membership in the early recovery and later recurrence classes.

Relationship with past study findings

Contrary to the widely held belief that MDD is a chronic and recurring disorder (Boland & Keller, 2009), our results suggest that 68-73% of MDD cases have a low probability of recurrence within the 5-10-year period following their initial diagnosis. This is consistent with the results of Eaton and colleagues (Eaton et al., 2008) who found that the majority of community MDD cases in the ECA experienced only a single lifetime MDD episode. It is inconsistent, however, with results from past studies of clinical

samples, which found that 60-75% of cases experienced a recurrence within 10 years (Keller & Boland, 1998; Solomon et al., 1997). It is possible that, due to sampling or selection methods, the participants in these previous studies represent the most severe end of the MDD spectrum even among clinical cases. If this is the case, then past studies of course in clinical samples may have overestimated the recurrence rates among clinical cases. It is also possible, however, that our estimate of the proportion of MDD cases with an early recovery course are somewhat inflated, as it may include individuals who received a single MDD diagnosis in error. Overall, the validity of MDD diagnoses in the register is quite good: 75% of individuals with a single MDD episode in the register also receive an MDD diagnosis when evaluated using the Schedules for Clinical Assessment in Neuropsychiatry (SCAN) (Bock, Bukh, Vinberg, Gether, & Kessing, 2009). However those that were misdiagnosed would be disproportionately placed in the early recovery class relative to the other classes, which may have somewhat inflated our estimate of the size of this class.

Although our estimate of the number of MDD cases with a recurrent course differs from estimates in previous studies, our estimates of the number of cases with a *chronic* course (3.6-8.3%) were surprisingly similar. In the CDS, 12% of patients were chronically ill for at least 5 years and 7% were chronically ill for at least 10 years (Keller & Boland, 1998; Mueller et al., 1996). The Zurich and ECA studies reported rates of chronic illness between 13 and 15% (Eaton et al., 2008; Keller & Boland, 1998). These estimates are surprisingly consistent with the current findings, especially considering that these studies measured symptoms directly whereas we relied on treatment as an indicator of illness. In light of this, we are in agreement with the conclusions of Keller and Boland

that “there exists a core of individuals with unipolar major depression who remain ill for a minimum of 15 years (Keller & Bollond, 1998; pg. 350).

Our findings with regards to predictors of course trajectory class membership are largely consistent with results from previous studies. Female gender was associated with a more severe depression trajectory, which is consistent with results from both group-based trajectory models of depression in general population samples (see chapter 2) and time-to-event studies in clinical samples (Kessing, Andersen, & Mortensen, 1998; Mueller et al., 1999). The finding that a previous dementia diagnosis was associated with a course trajectory characterized by more prolonged illness among late-onset MDD cases is also consistent with previous findings (Beekman et al., 2002). Our finding that parental history of different psychiatric disorders predicts different MDD course trajectories is new, predominantly because this is the first study to examine predictors of course trajectory in a dataset with the variables necessary to investigate that research question.

With the exception of dementia, we did not find associations between the type or burden of somatic illness and course trajectory class membership. This is inconsistent both with results from group-based trajectory models in non-clinical samples (Byers et al., 2012; Hsu, 2012; Kuo, Lin, Chen, Chuang, & Chen, 2011; Liang, Xu, Quiñones, Bennett, & Ye, 2011) and with the vascular depression hypothesis (Alexopoulos et al., 1997). One possible explanation is that vascular disease effects the incidence of MDD, but not the course. Another possible explanation is that somatic illness effects trajectories of depressive symptoms, but for whatever reason this does not translate into differences in trajectories of MDD treatment. Perhaps individuals with comorbid somatic

illness are able to receive depression treatment from their primary care doctors, and therefore do not require additional specialized psychiatric care.

5.4 Implications for public health and future directions for research

Major depressive disorder has been identified as one of the most common and burdensome health conditions worldwide (Ferrari et al., 2013; Kessler et al., 2003; Kessler, Chiu, Demler, Merikangas, & Walters, 2005; Kessler et al., 2005). The results of this study suggest that while MDD is indeed very common, the public health burden of MDD may be disproportionately attributable to a relatively small subset of cases. If this is indeed the case, it is imperative that we develop methods for identifying these individuals as early as possible so that public health resources can be allocated in an effective manner. The results of the current studies suggest that characteristics such as gender, severity of the initial episode, previous dementia diagnosis and parental history of psychiatric disorders may prove useful for developing a prediction model for identifying these cases at the start of their illness. Such a model could be invaluable for public mental health, therefore future research should investigate this possibility further.

The results of these studies also have implications for our understanding of the underlying genetic etiology of MDD. To date, genetic studies have failed to identify any variants significantly associated with risk for MDD (Ripke et al., 2013), despite the fact that 30-40% of the population-level variation in depression is attributable to genetic factors (Sullivan, Neale, & Kendler, 2000). Exploring phenotypic heterogeneity, including heterogeneity in long-term course, has been suggested as a direction for future genetic studies (Levinson et al., 2014). In paper 2, we found that different psychiatric diagnoses in parents predicted different MDD course trajectories in offspring. This

suggests that observable differences in course trajectory may be indicative of underlying differences in genetic etiology. It may be that different genetic variants confer risk for different MDD subtypes, in which case combining all MDD cases into a single group might obscure the signal of genetic effects. Future studies should examine genetic risk separately in MDD cases with different long-term course trajectory patterns to determine whether this is in fact the case.

In paper 2, we found that parental history of depression or anxiety predicted membership in the later recurrence class, while parental history of psychotic illness predicted membership in the chronic illness class. Previous work conducted by members of the Psychiatric Genomics Consortium (PGC) suggested an overlap in SNP-based heritability for schizophrenia and MDD, as well as bipolar disorder and MDD (Lee et al., 2013). It is possible that there is a subtype of MDD characterized by a more chronic course that shares a genetic basis with schizophrenia, while another subtype of MDD characterized by a fluctuating course shares a genetic basis with anxiety and/or bipolar disorder. Future research should investigate this possibility further.

In addition to the directions for future research described above, it would be worthwhile to delve further into the early recovery class and determine how many of these individuals are truly recovered and how many receive antidepressant medication from their primary care doctors during the follow-up period. The Danish Prescription Register (Kildemoes et al., 2011), which includes information on all medications prescribed in Denmark since 1994, could be used to address this research question. This registry could also be useful for further exploration of the association between somatic disease and MDD course trajectory in late onset cases. With the exception of dementia,

we did not find promising evidence to suggest an association between somatic diagnoses and MDD course trajectory class membership. It could be that many older adults in the sample have hypertension or hypercholesterolemia severe enough to warrant medication use, but not severe enough to lead to hospitalization. Data on primary care prescriptions could allow us to better classify individuals as having or not have vascular pathology, which could potentially allow us to detect, or rule out, an association between vascular pathology and course trajectory class membership with greater certainty.

5.3 Strengths and Limitations

The greatest strengths of these studies are the size and representativeness of the Danish registry dataset. The size of the registry (~8 million people) means these studies had a large amount of statistical power to detect effects. This is of particular importance when conducting group-based trajectory models, as properly characterizing small groups within a population can require very large sample sizes. An additional benefit of the size of the registry is that it allowed us to impose selection criteria to improve the internal validity of the results (such as restricting the sample to individuals with no history of bipolar or schizophrenia diagnoses) without severely compromising statistical power. In addition, the Danish registry has longitudinal data spanning decades, with records of admission and discharge dates accurate to the day. This enabled us to vary the time metric for the trajectory analyses (1 year, 6 months) as needed. The fact that healthcare is free and readily accessible in Denmark, and that all psychiatric and hospital visits are included in the registry, means that the probability of selection bias is low.

Limitations of these studies have already been discussed in previous chapters, but to briefly reiterate, the greatest weaknesses of these studies are as follows: first, we were

unable to measure illness directly. Instead, as with all register-based research, we rely on recorded treatment as an indicator of illness. This creates a potential source of sampling bias, as milder MDD cases are less likely than moderate or severe cases to receive specialized psychiatric treatment. It also raises the question of whether we are actually measuring trajectories of illness course, or simply trajectories of treatment.

There are certain to be other variables besides symptoms which influence the probability of treatment in Denmark. However many of the barriers that prevent people from seeking treatment in the United States and other parts of the world are either non-existent in Denmark, or far less prevalent. The fact that healthcare is free in Denmark removes financial barriers to treatment, which are a large issue in the United States. There is no shortage of mental health treatment providers in Denmark, as there are in many developing countries, which removes another potential barrier to access. According to the WHO World Health Statistics report (2013), Denmark has 1.4 psychiatrists per 10,000 people, one of the highest rates in the world (the United States has 0.8 per 10,000 people). In addition, Denmark is a small and heavily urbanized country, meaning that travel distance is unlikely to present a barrier to access even in more rural areas. Finally, Denmark is ethnically and culturally homogenous, which decreases the likelihood of systematic differences in treatment seeking behaviors. During the time frame of the current studies (1995-2007), 91-94% of the population in Denmark were of Danish ancestry (Denmark Statistics, 2015). In 2007, 83% of the population were members of the National Church of Denmark (Denmark Statistics, 2015).

In light of all of these factors, we believe that the largest variable influencing whether someone will receive treatment for MDD in Denmark is the extent to which they

are ill. As a result, treatment can be considered a good, if imperfect, indicator of illness. It is therefore possible to make inferences about the underlying illness course based on information derived from treatment records.

A final limitation of these studies is that we did not have information on treatments such as medications or psychotherapy. However, because all of the admissions analyzed in these studies took place within 7 year time spans (1995-2002 and 2000-2007), it is reasonable to assume that all patients had access to the same medications and treatments. In addition, previous research on the course of affective disorders in Denmark suggests that access to antidepressant medications does not influence course patterns (Kessing, Hansen, & Andersen, 2004). We also included calendar year of first diagnosis in the models in an attempt to control for any secular trends.

5.6 Conclusions

In conclusion, the results of these studies reaffirm that long-term trajectories of depression are heterogeneous. Group-based trajectory models provide a statistical method to identify subgroups of individuals following distinct trajectories of depression over time, characterize trajectory patterns separately within each group, and identify predictors of course trajectory class membership. Although the majority of previous studies examining heterogeneity in depression trajectories using these methods have focused on general-population samples, the current studies demonstrate that this method can also be used to successfully characterize trajectories of illness course among individuals with a clinical diagnosis of MDD.

5.7 References

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APPENDIX A: *ICD-8 and ICD-10 diagnostic codes used to characterize major depressive disorder*

Code		Diagnosis Name
ICD- 8	**ICD-10**	
296.0		Involutional melancholia
296.2		Manic depressive psychosis, depressed type
298.0		Reactive depressive psychosis
300.4		Depressive neurosis
	F32.0	Depressive episode, mild
	F32.1	Depressive episode, moderate
	F32.2	Depressive episode, severe without psychotic features
	F32.3	Depressive episode, severe with psychotic features
	F32.8	Depressive episode, other
	F32.9	Depressive episode, NOS
	F33.0	Recurrent depressive disorder, current episode mild
	F33.1	Recurrent depressive disorder, current episode moderate
	F33.2	Recurrent depressive disorder, current episode severe without psychotic features
	F33.3	Recurrent depressive disorder, current episode severe with psychotic features
	F33.8	Recurrent depressive disorder, other
	F33.9	Recurrent depressive disorder, NOS

APPENDIX B: *Exclusionary ICD-8 and ICD-10 diagnostic codes*

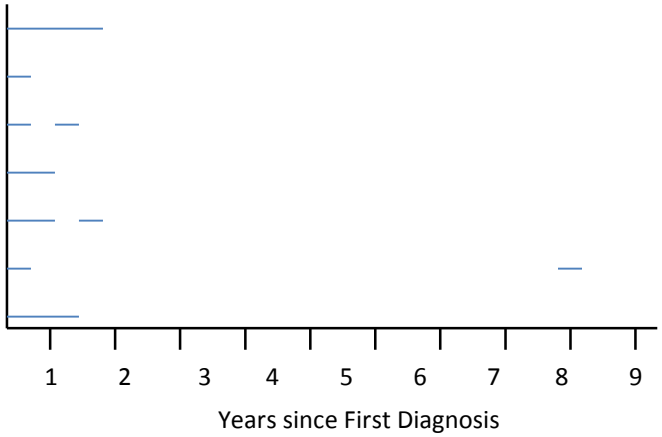
ICD Code		Diagnosis Name
ICD-8	**ICD-10**	
296.1		Manic depression psychosis, manic type
296.3		Manic depression psychosis, circular type
298.1		Reactive excitation
	F30.0	Hypomania
	F30.1	Mania without psychotic symptoms
	F30.2	Mania with psychotic symptoms
	F30.8	Other manic episodes
	F30.9	Manic episodes NOS
	F31.0	Bipolar affective disorder, current episode hypomanic
	F31.1	Bipolar affective disorder, current episode manic without psychotic symptoms
	F31.2	Bipolar affective disorder, current episode manic with psychotic symptoms
	F31.3	Bipolar affective disorder, current episode mild or moderate depression
	F31.4	Bipolar affective disorder, current episode severe depression without psychotic symptoms
	F31.5	Bipolar affective disorder, current episode severe depression with psychotic symptoms
	F31.6	Bipolar affective disorder, current episode mixed
	F31.7	Bipolar affective disorder, currently in remission
	F31.8	Other bipolar affective disorder
	F31.9	Bipolar affective disorder NOS
295.3	F20.0	Paranoid schizophrenia
295.1	F20.1	Hebephrenic schizophrenia
295.2	F20.2	Catatonic schizophrenia
	F20.3	Undifferentiated schizophrenia
	F20.4	Post-schizophrenic depression
295.6	F20.2	Residual schizophrenia
295.0	F50.6	Simple schizophrenia
	F20.8	Other schizophrenia
	F20.9	Schizophrenia NOS
295.5	F21.9	Schizotypal disorder/Latent schizophrenia
	F22.0	Delusional disorder
	F22.8	Other persistent delusional disorder
	F22.9	Persistent delusional disorder NOS
	F23.1	Acute polymorphic psychotic disorder with symptoms of schizophrenia
295.4	F23.2	Acute schizophrenia-like psychotic disorder

	F23.3	Other acute predominately delusional psychotic disorder
	F23.8	Other acute and transient psychotic disorder
	F23.9	Acute and transient psychotic disorder NOS
295.7		Schizoaffective disorder
	F25.0	Schizoaffective disorder, manic type
	F25.1	Schizoaffective disorder, depressed type
	F25.2	Schizoaffective disorder, circular type
296.8	F25.8	Other schizoaffective disorder/affective psychosis
296.9	F25.9	Schizoaffective disorder NOS
	F28.9	Other non-organic psychotic disorder
299.0	F29.9	Unspecified non-organic psychosis
298.9		Reactive psychosis, NOS

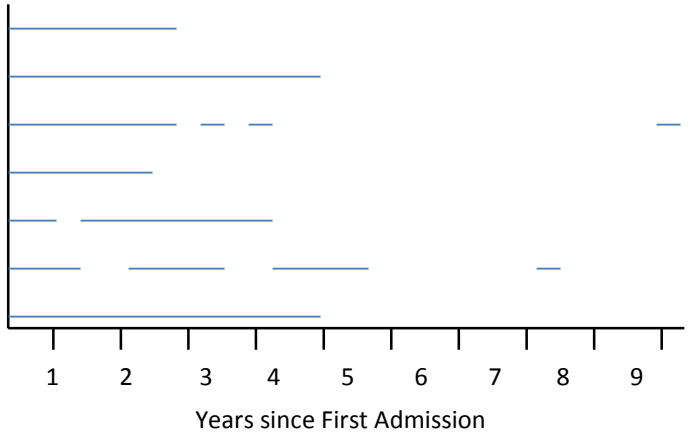
NOS = not otherwise specified.

APPENDIX C: *Within-class variation in individual-level treatment patterns*

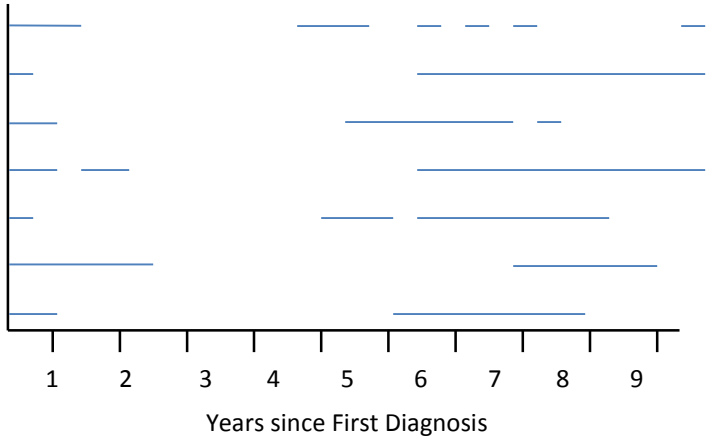
a) Individual variation within class 1



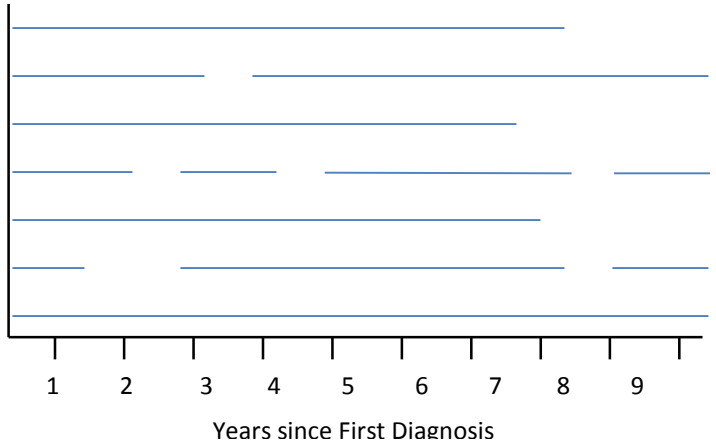
b) Individual variation within class 2



c) Individual variation within class 3



d) Individual variation within class 4



Note. The patterns depicted in these figures are representations of individual admission trajectories, not actual individual-level data

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PUBLICATIONS

1. **K. L. Musliner,** B. B. Trabjerg, B. L. Waltoft, T. M. Laursen, P. B. Mortensen, P. P. Zandi and T. Munk-Olsen. Parental history of psychiatric diagnoses and unipolar depression: a Danish National Register-based cohort study. Psychological Medicine, available on CJO2015. doi:10.1017/S0033291715000744.
2. **Musliner, K. L.,** Seiffudin, F., Judy, J., Piroohznia, M., Goes, F. & Zandi, P. P. (2014). Polygenic risk, stressful life events and depressive symptoms in older adults: A polygenic score analysis. *Psychological Medicine,* available on CJO2014. doi:10.1017/S0033291714002839.

3. **Musliner, K. L.** & Singer, J. B. (2014). Emotional support and adult depression in survivors of childhood sexual abuse. *Child Abuse & Neglect*, 38(8), 1331-1340.
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In Review:

1. Laursen, T. M., **Musliner, K. L.,** Benros, M. E., Vestergaard, M, & Munk-Olsen, T. *Mortality and Life expectancy in persons severe unipolar depression.* (In review at Psychological Medicine).
2. Goes, F. S, Liebers, D., Pirooznia, M., Seiffudin, F., **Musliner, K. L**., Zandi, P. P. *Polygenic risk of schizophrenia and cognition in a population-based sample of older adults.* (In review at Schizophrenia Bulletin).

In Preparation:

1. **Musliner, K. L.,** Munk-Olsen, T., Laursen, T. M., Zandi, P. P., Eaton, W. W. & Mortensen, P. B. *Patterns and predictors of 10-year course trajectories of major depressive disorder in the Danish psychiatric register.* (In preparation for submission to the American Journal of Psychiatry).
2. **Musliner, K. L.,** Munk-Olsen, T., Zandi, P. P. *Heterogeneity in long-term trajectories of depressive symptoms: Evidence from group-based trajectory models.* (In preparation for submission to the Journal of Affective Disorders).
3. **Musliner, K. L.,** Munk-Olsen, T., Laursen, T. M., Zandi, P. P., Mortensen, P. B. & Eaton, W. W. *Patterns and predictors of 5-year course trajectories of late-onset major depressive disorder: A Danish register-based study.* (In preparation for submission to the International Journal of Geriatric Psychiatry).
4. Dahl, S. K., Laursen, J. T., **Musliner, K. L.,** Petersen, L., Ubbesen, M. B., Mortensen, P. B., Munk-Olsen, T. *The influence of early adverse life events on risk of unipolar depression in adolescence and adulthood.*

ABSTRACTS / CONFERENCE PRESENTATIONS

Musliner, K. L. Trabjerg, B. B., Waltoft, B. L., Laurson, T. M., Mortensen, P. B., Zandi, P. P. & Munk-Olsen, T. (2015, June 14-18). Parental history of psychiatric diagnoses and unipolar depression: A Danish national register-based cohort study. Poster to be presented at the 12th World Congress of Biological Psychiatry, Athens, Greece.

Musliner, K. L., Munk-Olsen, T., Laursen, T. M., Zandi, P. P., Eaton, W. W., Mortensen, P. B. (2015, March 5-7). Patterns and predictors of 10-year course trajectories of major depressive disorder. Poster presented at the 105th Annual meeting of the American Psychopathological Association, New York City, NY.

Dahl, S. K., Larsen, J. T., **Musliner, K. L.,** Ubbesen, M. B., Mortensen, P. B., Munk-Olsen, T. (2015, March 5-7). The influence of early adverse life events on risk of unipolar depression in adolescence and adulthood. Poster presented at the 105th Annual meeting of the American Psychopathological Association, New York City, NY, USA.

Musliner, K. L., Seifuddin, F., Judy, J., Pirooznia, M., Elhaik, E., Goes, F. & Zandi, P. (2013 October 17-21). Genetic risk, life stress and depression: Searching for polygene-by-environment interactions. Poster presented at the XXIst World Congress of Psychiatric Genetics Conference, Boston, MA, USA.

Musliner, K. L. & Singer, J. B. (2012, July 27). Assessing the Role of Emotional Support as a Protective Factor against Depression in Adult Survivors of Childhood Sexual Abuse. Oral session presented at the 10th Add Health Users Conference, Bethesda, MD, USA.

Singer, J. B. & **Musliner, K. L.** (2012, July 27). Effects of youth suicidal behavior on perceived connection to mother, father, and family. Oral session presented at the 10th Add Health Users Conference, Bethesda, MD, USA.

Gordon, T.F., Bass, S.B., Ruzek, S.B., Ward, S., Paranjape, A., Lin, K., Meyer, B., Wolak, C., Rovito, M. J., Britto, J., Abedin, Z., Rovito, G.M., & **Musliner, K.L.** (2010, November 10). Encouraging low-literacy African Americans to be screened for colorectal cancer: An experimental comparison of "usual care" materials with a customized touch-screen tutorial. Oral session presented at the 138th Annual Meeting of the American Public Health Association (APHA), Denver, CO, USA.

Musliner, K.L. (2010, October 4-5). Childhood sexual assault and gender differences in adult depression: An analysis of state level data. Poster session presented at the Annual Pennsylvania Public Health Association (PPHA) Conference, Harrisburg, PA, USA.

Goldbacher, E.M., Oliver, T.L., Monks, C., Dilks, R.J., **Musliner, K.L.,** Klotz, A.A., Vander Veur, S.S. & Foster, G. (2009, October 24-28). Emotional Eating in Obese Treatment Seekers. Poster session presented at the 27th Annual Scientific Meeting of The Obesity Society, Washington D.C., USA.

Vandersall, E., Minaya, L., **Musliner, K.L.,** & Boltz, M. (March 22-25, 2007). Cross-modal influences on impression formation. Poster session presented at the Annual Eastern Psychological Association (EPA) Convention, Philadelphia, PA, USA.